

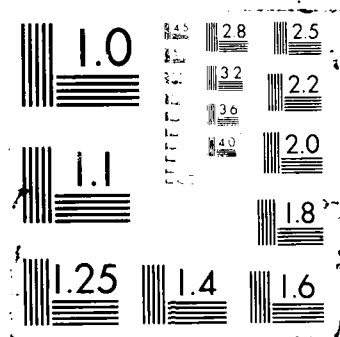
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CHEMOTHERAPY OF RODENT MALARIA

FINAL REPORT

WALLACE PETERS MD DSc

JULY 1985

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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1. INTRODUCTION

During the first half of the period since the submission of the Final Report for DAMD-17-83-G-9518, the emphasis of our studies was on vector orientated investigations of causal prophylactic, gametocytocidal and sporontocidal activity. However, in August 1984, it became necessary to close the Winches Farm insectaries as the Anopheles stephensi colony had become infected with a microsporidian parasite Pleistophora (Vavraia) culicis. Since there is no practical way of eliminating this organism from an infected colony, it was decided that this essential closure should be used as an opportunity to refurbish the insectaries and install an effective environmental control system. During the course of this work, it was found that a considerable amount of building repair was needed as the roof timbers were affected by dry rot. This work is now complete and it is anticipated that mosquito linked studies will recommence within the next two months.

The latter part of the contract period and the three months between the conclusion of the extension period and the commencement of the new contract has been concerned primarily with blood schizontocidal activity and in particular with studies on the development of resistant strains. Rodent malaria strains resistant to Halofantrine and to quinine have been developed and these will be included in future blood schizontocidal activity tests.

2. ADMINISTRATIVE EVENTS

Staff employed on US Army funds are as follows:

Senior Technologist/ Research Assistant	- Mr B L Robinson	50 % time
Junior technician	- Ms A West	100 % time
Junior technician	- Ms J R Cox	100 % time
Secretary	- Mrs T Sargeaunt	25 % time

Other staff associated with the project but paid from from London
School sources are:

Professor W Peters (Principal Investigator)	20% time
Dr D C Warhurst (Biologist)	20% time
Dr D S Ellis (Electron Microscopist)	10% time
Dr W E Ormerod (Biologist-Pharmacologist)	20% time

In the period covered by the contract we have received seven compounds from WRAIR (including an additional supply of Halofantrine for resistance studies).

The collection of cryopreserved strains of rodent malaria continues to expand with the inclusion of strains resistant to Halofantrine, quinine and artemisinin. In addition, we are producing clones of our standard strains which are being included. Lysates have now been prepared from many of the stabilates for use in isoenzyme characterization studies. When completed, these studies will allow us to use defined cloned strains in our test systems.

Currently we have a battery of thirteen strains (derived from Plasmodium berghei or P.yoelii), which are resistant to

standard antimalarials, and one drug-sensitive P.berghei available for use in blood schizontocidal tests. Studies involving mosquito and exo-erythrocytic stages will in future employ P.yoelii 17X as well as P.y.nigeriensis.

An official visit was made to the School and Field Station by Dr Ho Chung and Ms Maxine Losee of USAMRDC in June 1984.

A close liaison has been maintained between the Principal Investigator and Colonel Davidson of WRAIR.

3. CHEMOTHERAPY STUDIES

3.1 Blood schizontocides

Data are summarised in Table 15 and detailed report sheets are appended as Tables 16 through 21.

3.1.1 WR 251855 AA

This lepidine, an analogue of primaquine, is very active against the drug-sensitive N strain of P.berghei possessing an ED₉₀ of 0.67 mg/kg X 4 sc. Further studies, involving our full battery of resistant lines, are to be carried out and results will be included in a subsequent report.

3.1.2 BK 74491 (WR number not known)

This compound has an ED₉₀ of 3.4 mg/kg X 4 sc against P.berghei N strain, a level of activity comparable with that of primaquine. Further studies involving the resistant lines are scheduled.

3.1.3 BK 73127 (WR number not known)

BK 73127 is slightly more active than the preceding compound against the N strain with an ED₉₀ of 2.1 mg/kg X 4 sc. Data from tests with resistant lines will be included in a later report.

3.1.4 Amodiaquine

In view of a recent resurgence of interest in this compound, it was decided to examine amodiaquine for activity against some of our resistant lines. In the drug sensitive N strain amodiaquine has an ED₉₀ of 2.7 mg/kg X 4 sc, a value very similar to that of chloroquine.

When used against the moderately chloroquine-resistant NS line, the ED₉₀ value increased significantly to 25.5 mg/kg - a resistance factor of 9.4. Our highly chloroquine-resistant RC strain was also highly resistant to amodiaquine, the resistance factor being considerably in excess of 22 (ED₉₀ = >60 mg/kg). A similar result was obtained with the quinine-resistant N/1923 strain where the ED₉₀ was also in excess of 60 mg/kg.

The mefloquine-resistant N/1100 line was also markedly insensitive to amodiaquine and the ED₉₀ against this strain was 75 mg/kg X 4 sc. This represents a resistance factor of 27.8 for the N/1100 when compared with N strain.

3.2 Causal prophylaxis

Causal prophylactic test data for 8-aminoquinolines and quinine analogues are summarised in Tables 1 and 2, detailed results from all tests are included in Tables 22 through 34.

3.2.1 Putative metabolites and analogues of primaquine

Results of earlier studies on all of the above compounds, with the exception of RCGJM-97, have been reported previously and the current tests have been performed to confirm earlier conclusions or to extend the dose range. The results obtained with WR 6890 and 15081 confirm our earlier findings of activity and illustrate the slightly lower level of activity of WR6890.

TABLE 1 A summary of causal prophylactic activity in some 8-aminoquinolines.

LON	WR Number	MFED	Residual activity
1801	15081	10 - 30	Nil at 30
1802	6890	30 - 100	Nil at 100
1877	199508AD	> 100	Nil at 100
1783	ANC-IX-19	Inactive at 100	Nil at 100
1908	RCGJM-97	30 - 100	Present at 30

MFED = Minimum fully effective dose. All doses expressed in mg/kg.

WR 199508 AD and the McChesney compound, ANC-IX-19, have been examined at higher dose levels and slight activity at 100 mg/kg is demonstrable with WR 199508 AD. No evidence of activity was found at this dose with ANC-IX-19.

A further compound, RCGJM-97 (3-bromo-primaquine, received from Dr McChesney) was found to be fully active at 100 mg/kg but this activity is at least partially due to the residual action of the compound.

3.2.2 Quinine analogues

These four quinine analogues showed no significant activity at 100 mg/kg in our preliminary tests (previously reported). In the current studies at higher dosage, Ph 4007 and pH 4901 show activity at 300 mg/kg associated with residual activity in the

case of Ph 4007. Neither Ph 4017 nor Ph 4900 show any activity at 300 mg/kg.

TABLE 2 A summary of causal prophylactic activity of four quinine analogues.

LON	WR Number	MFED	Residual activity
1884	Ph 4007	> 300	Nil at 300
1885	Ph 4017	Inactive at 300	Nil at 300
1886	Ph 4900	Inactive at 300	Nil at 300
1887	Ph 4901	> 300	Nil at 300

3.2.3 Floxacrine analogue

The floxacrine analogue, WR 250547 AA, had previously been reported to be fully active at 3 mg/kg with evidence of residual activity being present. From the new data presented here it is apparent that residual activity is the major component in the overall activity. At a dose of 1 mg/kg the residual element accounts for all the demonstrable activity. The minimum fully effective dose in the causal prophylaxis test is the same as that of floxacrine (1.0 - 3.0 mg/kg x 1 sc).

3.2.4 Antibiotics

In the preliminary causal prophylactic test, spiramycin has a minimum fully effective dose of 30 - 100 mg/kg. Lincomycin hydrochloride was less active (MFED = > 100 mg/kg). Both of these compounds are to be re-examined, when causal prophylactic testing recommences, to establish the presence or absence of residual

activity.

3.3 Gametocytocidal activity

Data from gametocytocidal activity tests are summarised in Tables 3 to 7 and detailed results are given in Tables 35 through 61. An innovation in this test system is the inclusion of a GD (gametocytocidal dose)₅₀ and GD₉₀ obtained from a dose response curve plotted on log : probit graph paper. The GD₉₀ is compared with that of primaquine and expressed as a Primaquine Index (PI₉₀).

3.3.1 8-aminoquinolines

Twelve 8-aminoquinolines, including primaquine diphosphate, have been examined in the gametocytocidal activity test. Primaquine was included as a reference standard for use with all tests and was found to have a GD₉₀ of 33 mg/kg. This value has been used throughout for calculation of Primaquine Indices.

WR 182234 and WR 211814 were found to be almost as active as primaquine with PI₉₀ values of 0.9 and 0.6 respectively. WR 228708 was the only other 8-aminoquinoline to show a reasonable degree of activity (PI₉₀ = 0.24). The remaining eight compounds in this group were all appreciably less active.

TABLE 3 Gametocytocidal activity of 8-aminoquinolines.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
2975AW ¹	BJ 08241	1711	1.3	33.0	1.0
182234	BE 17580	1720	12.3	38.5	0.86
211814	ZP 12775	1721	8.0	59.0	0.56
215295	ZN 43444	1722	230	1100*	0.03
238605	BH 69990	1727	135	2700*	0.01
243789	BJ 08189	1728	150	950*	0.03
246315	BJ 45691	1729	27.0	1100*	0.03
247705	BJ 51779	1730	300	3900*	<0.01
248412	BJ 59202	1731	>300	>>300	<<0.1
237375	BH 58120	1732	60.0	3500*	<0.01
228708	BG 66798	1733	36.0	138	0.24
194343	ZN 41968	1751	>300	>>300	<<0.1

¹ Primaquine dipnosphate; * = interpolated graphically

3.3.2 Primaquine metabolites

TABLE 4 Gametocytocidal activity of some primaquine analogues.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
ANC-IX-19 ¹	(McChesney)	1783	180	440	0.08
249725	BK 69990	1931	NA100	-	-
15081	AY 15653	1801	>300	>>300	<<0.1
6890	BK 12713	1802	100	340	0.1
RCGJM-53 ²	(McChesney)	1810	105	460	0.07
199508 AD	BK 56500	1877	220	3250*	0.01

¹ = WR 249725; ² = WR 199507 (5-hydroxyprimaquine)

NA = no activity; * = interpolated graphically

None of the six primaquine metabolites examined possess any marked degree of gametocytocidal activity. The best of these, WR 6890, had a PI₉₀ of 0.1.

3.3.3 Quinine analogues

TABLE 5 Gametocytocidal activity of some quinine analogues.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
Ph 4007	BK 64306	1884	31.0	365	0.09
Ph 4017	BK 64315	1885	20.0	90.0	0.37
Ph 4900	BK 64324	1886	13.5	92.0	0.36
Ph 4901	BK 64333	1887	>300	>>300	<<0.1

Our earlier observation of activity with the four quinine analogues has been confirmed in the current series of tests. The least active of the four was Ph 4901 and the flat nature of the dose response curve precluded us from obtaining a meaningful GD_{90} . A little more active was Ph 4007 with a GD_{90} of 365 (PI_{90} = 0.09) but Ph 4017 and Ph 4900 were very much more active. Ph 4017 had a GD_{90} of 90.0 mg/kg (PI_{90} = 0.37) and Ph 4900 had the same degree of activity with a GD_{90} of 92.0 mg/kg (PI_{90} = 0.36).

3.3.4 Floxacrine analogues

TABLE 6 Gametocytocidal activity of two floxacrine analogues.

WR	BN	LON	GD_{50}	GD_{90}	PI_{90}
245082	BK 02771	1752	70.0	2100*	0.02
246976	BK 02780	1753	11.0	255	0.13

* = interpolated graphically

Two floxacrine analogues, WR 245082 and WR 246976, have been examined for gametocytocidal activity. WR 246976 has approximately six times the activity of WR 245082 (PI_{90} values are 0.13 and 0.02 respectively).

3.3.5 Quinolines/quinoline-methanols

One quinoline-methanol, mefloquine, and two quinolines were tested in the gametocytocidal test system. Neither of the quinolines, WR 44450 AD and WR 102796 AD, show high levels of activity, and although mefloquine was active in this system, the GD_{90} level was not reached in this test. Further investigations of mefloquine and other amino-alcohols are planned.

TABLE 7 Gametocytocidal activity of mefloquine and two quinolines.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
44450 AD	AY 29540	1740	215	2000*	0.02
102796 AD	BC 78878	1741	34.0	>300	<0.1
142490 ¹	BH 10371	1100	11.0	>60	<0.55

¹ Mefloquine ; * graphically interpolated

3.4 Sporontocidal activity

Summarised results are included in Tables 8 through 14 and detailed test results are presented in Tables 62 through 101. As with the gametocytocidal test, it should be possible to quantify the sporontocidal effect and express it as a sporontocidal dose (SD₅₀ and SD₉₀) when an extended test is done. In the current report, however, we are presenting preliminary test data and activity in this single dose test can only be expressed qualitatively. Since no positive drug control has been included in this preliminary test series, and no extended dose range tests have yet been performed, the classification of activity is necessarily arbitrary. Further studies may indicate that other contributory factors, such as generalised cytotoxicity, are playing a significant part in oocyst suppression and the criteria currently employed in determining activity levels may require revision. Full tests, using an extended dose range and including pyrimethamine and/or cycloguanil as positive drug controls, will be performed on those compounds which have shown activity in the preliminary test.

3.4.1 8-aminoquinolines

TABLE 8 Sporontocidal activity of 8-aminoquinolines.

WR	BN	LON	ACTIVITY	% SUPPRESSION
225448 AG	BH 58522	1709	INACTIVE	15.1
5990	AG 99266	1715	ACTIVE	43.4
181023	BE 50003	1719	SLIGHTLY ACTIVE	39.1
182234	BE 17580	1720	INACTIVE	9.8
211814	ZP 12775	1721	SLIGHTLY ACTIVE	27.7
215295	ZN 43444	1722	ACTIVE	41.5
228000	ZN 81499	1723	INACTIVE	14.5
228583	ZN 78910	1724	ACTIVE	51.7
233627	BH 13989	1725	ACTIVE	58.5
235485	BH 35770	1726	ACTIVE	48.3
238605	BH 69990	1727	INACTIVE	21.3
243789	BJ 08189	1728	ACTIVE	44.9
246315	BJ 45691	1729	ACTIVE	55.1
247705	BJ 51779	1730	ACTIVE	67.1
248412	BJ 59202	1731	INACTIVE	1.7
237375	BH 58120	1732	INACTIVE	9.7
228708	BG 66798	1733	INACTIVE	23.1
242511 AA	BH 89438	1734	INACTIVE	0
242511 AB	BJ 78592	1736	ACTIVE	47.8
194343	ZN 41968	1751	SLIGHTLY ACTIVE	27.9
249725	BK 69990	1931	ACTIVE	57.4
251855 AA	BK 71178	1932	ACTIVE	39.8

A total of twenty-two 8-aminoquinolines have been examined in the preliminary screening test. Eight of these show no significant activity at the standard concentration (0.05%) used in this test. Three compounds (WR 181023, WR 211814 and WR 194343) show slight activity and the remaining ten compounds are active. None of the 8-aminoquinolines tested have been fully active at the dose used. The highest levels of activity were found with WR 249725 and WR 247705 which produced approximately 60 and 70 per cent suppression of oocysts respectively.

3.4.2 Putative primaquine metabolites

TABLE 9 Sporontocidal activity of some putative primaquine metabolites.

WR	BN	LON	ACTIVITY	% SUPPRESSION
199508 AD	BK 56500	1877	SLIGHTLY ACTIVE	29.0
199508	ZP 43350	1940	SLIGHTLY ACTIVE	30.7

Two samples of putative metabolites of primaquine have been submitted for sporontocidal activity testing. Both of these samples (WR 199508 AD and 199508) proved to be 6-hydroxy primaquine and gave almost identical results in the test, demonstrating slight activity.

3.4.3 Quinine analogues

All four of the quinine analogues submitted demonstrated a marked toxicity to mosquitoes, with Ph 4007 killing all of the mosquitoes exposed to the 0.05 per cent concentration used in our

preliminary test. The remaining three compounds also exhibited toxicity in varying degrees at this dose and, consequently, even the low level of activity shown by Ph 4900 must be regarded as probably resulting from a generalised cytotoxicity.

TABLE 10 Sporontocidal activity of some quinine analogues.

WR	BN	LON	ACTIVITY	% SUPPRESSION
Ph 4007	BK 64306	1884	LETHAL TO MOSQUITOES	
Ph 4017	BK 64315	1885	INACTIVE	0
Ph 4900	BK 64324	1886	ACTIVE	39.3
Ph 4901	BK 64333	1887	INACTIVE	0

3.4.4 Floxacrine analogues

TABLE 11 Sporontocidal activity of some floxacrine analogues.

WR	BN	LON	ACTIVITY	% SUPPRESSION
245082	BK 02771	1752	INACTIVE	0
246976	BK 02780	1753	SLIGHTLY ACTIVE	37.7
249684 AB	BK 51550	1870	ACTIVE	69.0
250548 AA	BK 51621	1871	SLIGHTLY ACTIVE	39.3
250547	BK 51630	1872	ACTIVE	58.6

Four of the five floxacrine analogues tested showed some degree of sporontocidal activity. The most active, WR 249684 AB,

showed almost 70 per cent suppression of oocysts, WR 250547 was nearly as active, producing approximately 60 per cent suppression, whilst WR 246976 and WR 250548 AA suppressed oocyst development by almost 40 per cent. The fifth analogue, WR 245082 was totally inactive at the test concentration, probably as a consequence of the extreme insolubility of this compound.

3.4.5 Mannich bases

TABLE 12 Sporontocidal activity of two Mannich bases.

WR	BN	LON	ACTIVITY	% SUPPRESSION
194965 AG	BG 56327	1707	ACTIVE	39.8
228258 AH	BJ 30663	1708	INACTIVE	9.2

No significant activity was demonstrable with WR 228258 AH but WR 194965 produced almost 40 per cent suppression.

3.4.6 Quinolines

TABLE 13 Sporontocidal activity of two quinolines.

WR	BN	LON	ACTIVITY	% SUPPRESSION
44450 AD	AY 29540	1740	SLIGHTLY ACTIVE	24.3
102796 AD	BC 78878	1741	SLIGHTLY ACTIVE	34.9

Both of the quinolines tested, WR 44450 AD and WR 102796 AD, were slightly active in the preliminary test.

3.4.7 Miscellaneous compounds

a) WR 9792 (guanyldrazone) demonstrated no significant

activity against oocysts of P.y.nigeriensis.

b) WR 158124 had a reasonable level of activity and caused approximately 40 per cent suppression of oocyst development.

c) WR 203659 (clindamycin) is totally inactive in this test system at the dose tested.

TABLE 14 Sporontocidal activity of three miscellaneous compounds.

WR	BN	LON	ACTIVITY	% SUPPRESSION
9792	AJ 63248	1716	INACTIVE	14.2
158124	ED 22997	1718	ACTIVE	40.6
203659	ZN 39913	1909	INACTIVE	0

3.5 Combination studies

The bulk of the studies on drug interactions in this department are carried out under the terms of a WHO contract. Since, however, some of the compounds employed were supplied originally to us by WRAIR, the relevant results are summarised here for information.

Detailed data sheets are appended as Tables 102 through 194 and isobolograms are shown in Figures 1 to 14.

3.5.1 Mefloquine/spiramycin

This combination appears to produce a low degree of synergism.

3.5.2 Mefloquine/tetracycline

This combination was at best additive when tested using fixed ratios.

3.5.3 Mefloquine/minocycline

An additive effect resulted from this combination.

3.5.4 Mefloquine/clindamycin

When tested using fixed ratios, this combination was found to be more than additive.

3.5.5 Halofantrine/spiramecin

There is some suggestion of enhancement of the activity of halofantrine when using a combination of these compounds.

3.5.6 Halofantrine/chloroquine

The results obtained with this combination are indicative of a substantial degree of antagonism. This situation, when taken together with the rapidity with which halofantrine resistance may be induced experimentally in a chloroquine-resistant strain of P. yoelii and the blood schizontocidal test data on the halofantrine resistant line (reported in 3.6), is strongly suggestive of a shared receptor site for the two compounds.

3.5.7 Halofantrine/primaquine

Marked antagonism also occurs between halofantrine and primaquine. This is reflected in a reduced sensitivity to

primaquine in halofantrine resistant lines (see 3.6).

3.5.8 Halofantrine/pyrimethamine

The use of this combination results in a reasonable degree of synergism.

3.5.9 Halofantrine/sulfadiazine

This combination produces no more than an additive effect.

3.5.10 Halofantrine/clindamycin

There is no evidence of anything more than an additive effect with this combination.

3.5.11 Halofantrine/spiramyacin

The combination of these two compounds apparently produces a degree of potentiation.

3.5.12 Halofantrine/tetracycline

At best an additive effect results from this combination and a further experiment is required to eliminate the possibility of antagonism.

3.5.13 Halofantrine/minocycline

This combination produces a clear synergistic response.

3.5.14 Floxacrine/cycloguanil

Although this combination has been claimed to be possibly synergistic in a patent claim (HOECHST AG 1979), the evidence

obtained in our test indicates that it is additive . Further studies are to be undertaken to resolve this contradiction.

3.5.15 Floxacrine/quinine

This combination also appears to have at best an additive effect and is possibly even slightly anagonistic, in spite of a patent claim (vide supra) for synergism.

3.5.16 Floxacrine/tetracycline

Results of our interaction study indicate an additive effect.

3.5.17 Floxacrine/erythromycin

There is at least an additive effect obtained with this combination and, possibly, slight synergism occurs.

3.5.18 Floxacrine/chloroquine

The combination of these two compounds produces a slightly antagonistic effect.

3.5.19 Floxacrine/primaquine

This combination produced an additive effect in our test system.

3.6 Development of drug resistance

During the period covered by this report, studies have been made on the acquisition of resistance by strains of rodent

malaria to two compounds, halofantrine and quinine, using our relapse technique.

In the case of halofantrine, resistant lines were developed from a drug sensitive strain of P.berghei (N strain) and also from the moderately chloroquine-resistant NS strain of P.yoelii. This latter strain is, however, insufficiently sensitive to quinine to allow the serial passage of the strain under drug pressure for the purpose of developing resistance since there is not a long enough delay produced by even the maximum tolerated dose to permit evaluation of change. Therefore, we developed quinine resistance only in the drug sensitive N strain.

3.6.1 Halofantrine resistance

Two lines of halofantrine resistant rodent malaria have been developed. The line derived from P.berghei N strain (N/HAL) showed a rapid acquisition of resistance to the maximum dose permitting recrudescence (5 mg/kg) with complete resistance being apparently reached by the eighth passage. This resistance was unstable as it was promptly lost as a result of freezing at this stage and it required a further six passages after retrieval from liquid nitrogen to restore this level of resistance. The strain was then passaged under drug pressure for eighteen more passages, during which time the resistance remained consistent, prior to the removal of drug pressure. When passaged without drug the delay to 2 % parasitaemia rapidly reverted to that of the original sensitive parent line (Figure 15).

The resistance level of the N/HAL strain was checked in the four day test at passage 31 and, at that stage, possessed a resistance factor of 2.8 ($ED_{90} \approx 3.6 \text{ mg/kg} \times 4 \text{ sd}$) compared with

the parent strain which had an ED_{90} of 1.3 mg/kg.

The NS derived strain, NS/HAL, showed an even greater propensity for developing resistance to halofantrine with almost complete resistance to a dose of 30 mg/kg being apparent after a single passage under drug pressure. This resistance was not lost in cryopreservation but withdrawal of drug pressure after 37 passages caused rapid reversion to the original level of sensitivity as measured by the 2 % delay time (Figure 16). Resistance was checked by the four day test technique at passage 35 and at that point the NS/HAL had a resistance factor of 13.2 (ED_{90} = 560 mg/kg, interpolated graphically). The parent NS strain had an ED_{90} of 42 mg/kg.

Both the N/HAL and the NS/HAL were also tested for sensitivity to chloroquine, primaquine, mefloquine and quinine in the four day test. There was a reduced sensitivity to each of these compounds in both strains.

These data are summarised in Table 195, together with those of the quinine-resistant line, and detailed reports are included in Tables 196 through 210.

3.6.2 Quinine resistance

Owing to the innate insensitivity of the NS strain to quinine, it was only possible to utilise the drug sensitive N strain for the development of a quinine-resistant line (N/1923). A preliminary experiment showed that the N strain would recrudesce following a single dose of 600 mg/kg of quinine given orally. Resistance to quinine developed relatively slowly, requiring more than thirty passages under drug pressure before a reasonably consistent, high level of resistance was attained. The

development of quinine resistance is depicted graphically in Figure 17.

The level of resistance in the N/1923 strain was assessed by the four day test for blood schizontocidal activity at passage 56. The parent strain was included as a direct comparison and it was found that the ED₉₀ of quinine in the parent strain was 85 mg/kg X 4 po, whilst in the N/1923 strain a dose of 600 mg/kg X 4 orally produced virtually no effect.

After withdrawal of drug pressure (Figure 18), the resistance level remained constant for eighteen passages before the strain began to revert to sensitivity. Even after fifty-two passages without drug pressure, this strain has still not stabilised as a completely sensitive line comparable with the parent strain.

3.7 Mode of action studies

A corollary to the idea that haemin, released during the digestion of haemoglobin, is a site for binding of antimalarial schizontocides is the proposition that resistance to these drugs may involve changes in quantity or structure of the protein(s) involved in the complexation of haemin as malaria pigment (Warhurst, 1981). We have investigated the composition of malaria pigment in two strains of P.falciparum, NF54 (chloroquine sensitive) and K1 (chloroquine-resistant), with the following results.

The major polypeptide detected on SDSPAGE was present in all preparations of both strains and had a molecular weight (M_r) of 14.3 ± 0.8 K in NF54 and 14.6 ± 0.55 K in K1. It comprised 73 and 78 per cent of the total Coomassie blue staining protein and 40 and 55 per cent of the total labelled (³H-phenylalanine) protein.

The metabolic labelling of this component in vitro indicates that it is parasite derived.

Another polypeptide was found in eighty per cent of NF54 and all K1 pigment preparations. The M_r values were 30 K and 29.7 ± 0.56 K respectively. This polypeptide comprised 13.4 per cent (NF54) and 3.9 per cent (K1) of total protein and 12.9 per cent and 11.6 per cent of total labelled protein. In addition, a third polypeptide was found in eighty per cent of preparations of both strains. This had a M_r of 66.6 ± 0.48 K in NF54 and 66.5 ± 0.05 K in K1 derived material. When labelled (K1 only) it had 2.5 per cent of the total radioactivity.

Depending on the preparation's purity and the stages labelled, other minor bands were seen with molecular weights of 73 - 76 K and 20 - 22 K. These were not consistently present and are considered to represent contamination of the pigment preparation with membranes, etc.

Purified pigment from NF54 and K1 strains was subjected to protein (Lowry) and haemin (pyridine haemochrome) estimations to determine the relative proportions of haemin and protein. Combined data from eight estimations indicated that the relative proportions in NF54 were 52.32 per cent protein plus 10.03 per cent haemin. Similar estimations on a series of six K1 pigment preparations gave a result of 45.11 per cent protein plus 2.32 per cent haemin.

A 14 K polypeptide was reported as being precipitated from P.falciparum schizont preparations by a (? monoclonal) antibody (TDR/IMMAL/SWG(6)84.3). This may be the same polypeptide that we are finding, which would seem to be the major haemin-binding protein of P.falciparum.

Yamada and Sherman (1979) reported a 15 K pigment associated polypeptide in P. lophurae, which they suggested was a degraded monomer of globin. This was probably also a parasite derived haemin-binding protein.

Our observations would indicate that haemin is released in the digestive vacuoles and is available in trace amounts to bind to blood schizontocides such as chloroquine and quinine.

Studies on the aminoacid composition of the 14 K polypeptide indicate marked differences between the chloroquine-sensitive NF54 and the chloroquine-resistant K1 strains of P. falciparum.

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5. APPENDICES

5.1 BLOOD SCHIZONTOCIDAL TEST DATA

Summary of Observations on Bacteriological and Low Test Data

LON	WR & BN	D	RC			N/1100			N/1923			ED		
			1	ED	90	1	ED	90	1	ED	90	1	ED	90
1932	251855AA BK 71178	0.25	0.67											
1956	SC BK 74491	0.6	3.4											
1957	SC BK 73127	0.5	2.1											
2022	SC Amodiaquine	0.8	2.7	25.5	9.4	>60	>222	750	378	>60	>222			

TABLE 15

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OR NUMBER LON 1932 PARASITE SUBSPECIES P. eugene

MAXIMUM TOLERATED DOSE (MTD) ..30... MG/KG X 4.

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

Br 7443;

1997-1998

MAXIMUM TOLERATED DOSE (mg/kg) 1000 mg/kg (4)

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

BK 73.27

[illegible]

MAXIMUM TOLERATED DOSE (MTD) 2.000 MG/KG / 4

Resistance factor : 10

205154700 43 200 100

35

SUMMARY OF ANTIMALARIAL DRUG TESTS
(Blood schizontocides)

TABLE 10

COMPOUND NAME

DR NUMBER ... AMODIAQUINE ... PARASITE (SUB)SPECIES ... *P. berghei* ...

FORMULATION ... Tween 80 / H₂O ... ROUTE OF ADMINISTRATION : SC / IP / PO / IV

MAXIMUM TOLERATED DOSE (MTD) > 600 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated $\frac{P \pm S}{Control \frac{P \pm S}{\times 100}}$
	0.1	5		-	94.4 \pm 2.7
	0.3	5		-	72.1 \pm 7.6
N	1.0	5	1	-	61.4 \pm 5.5
	3.0	5		-	37.0 \pm 3.3
	10.0	5		-	0.1 \pm 0.1
	30.0	5		-	0
	\emptyset	10		20.3	
ED ₅₀ (range) 0.8 (0.4 - 1.5)					
ED ₉₀ (range) 2.7 (1.3 - 5.4)					
	0.1	5		-	71.3 \pm 7.2
	0.3	5		-	55.5 \pm 4.6
	1.0	5		-	50.9 \pm 3.9
NS	3.0	5	1	-	43.3 \pm 2.8
	10.0	5		-	14.0 \pm 4.2
	30.0	5		-	9.3 \pm 2.7
	60.0	5		-	7.8 \pm 2.6
	\emptyset	10		20.9	
ED ₅₀ (range) 0.6 (0.3 - 1.4)					
ED ₉₀ (range) 25.5 (11.5 - 54)					
Resistance factor I ₉₀ 9.4					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
- DRUG: Amodiaquine -

Table 20

COMPOUND NAME

DR NUMBER Amodiaquine PARASITE (SUB)SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/42/P0/IV

MAXIMUM TOLERATED DOSE (MTD) > 60 MG/KG X 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR%
	1.0	5		-	100
	3.0	5		-	84.7 ± 12.2
RC	10.0	5	1	-	95.6 ± 1.5
	30.0	5		-	65.7 ± 17.7
	60.0	5		-	62.3 ± 15.0
	Ø	10		7.7	
ED ₅₀ (range) > 60					
ED ₉₀ (range) > 60					
Resistance factor I ₉₀ > 22.2					
	3.0	5		-	100 ± 2.5
	10.0	5		-	44.4 ± 4.4
N 1100	30.0	5	1	-	30.4 ± 3.9
	60.0	5		-	20.0 ± 5.3
	Ø	10		10.8	
ED ₅₀ (range) 9.5 (6.0 - 18.5)					
ED ₉₀ (range) 75.0 (49.0 - 150)					
Resistance factor I ₉₀ 27.8					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

- 140 - 21

OR NUMBER AMODIAQUINE PARASITE (SUB)SPECIES P. cagnei

FORMULATION : Tween 80 / H₂O... ROUTE OF ADMINISTRATION : SC/ID/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 60..... MG/KG X 4..

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

5.2 CAUSAL PROPHYLACTIC TEST DATA

SUMMARY OF CAUSAL PROPHYLACTIC TESTS

PRINCIPAL INVESTIGATOR: PROFESSOR W. J. LINTERS
DEPARTMENT OF MEDICAL PROTOZOLOGY
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

DATE: 26.3.84

LAB. NO. 2624

WV 15081

BOTTLE NO: BK 12713

PARASITE: *P. yoelii*

STRAIN: NIG

TIME AFTER INFECTION: 2 HOURS

INOCULUM RATE	ACTIVITY VALUES			COMMENT
	Sporozoite and blood infected	Sporozoite and blood infected (a)	Residual activity (d-e)	
5/5	5/5	4.87	0	INACTIVE
3/3	3/3	4.61	0	INACTIVE
2/3	3/3	8.20	0	ACTIVE
0/3	3/3	14.00	0.04	FULLY ACTIVE

10.0 - 30.0
30.0

ORIGINAL INVESTIGATOR: EPIDEMIOLOGICAL
DEPARTMENT: Medical Microbiology
UNIVERSITY OF BIRMINGHAM

DATE: 26.3.84

CAUSAL PROPYLAXIS TEST NO: 2624

BOTTLE NO: AY 15653

WR 6890

TIME AFTER INJECTION: 7 HOURS

ROUTE: sc ~~4444~~FORMULATION: Tween 80/H₂O

STRAIN: N16

PARASITE: *P. yoelii nigricans*

HOST: ♂ HM mice

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (a)	Sporozoite and blood infected (c)	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a-d-c)	
Ø	5/5	5/5	4.87 (b)	2.92 (c)				
10.0	3/3	3/3	4.89 (b)	2.90 (c)	0.02	0	NUL	INACTIVE
30.0	2/3	3/3	>7.90 (b)	3.25 (c)	>3.03	0.33	>2.70	ACTIVE
100.0	0/3	3/3	>14.00 (b)	2.93 (c)	>9.13	0.01	>9.12	FULLY ACTIVE

TABLE 21

SPOROZOITE ACTIVITY INDEX: 30.0 - 100

SPOROZOITE ACTIVITY: 50

~~4444~~ AT 100

GMP 2% P AT

PRINCIPAL INVESTIGATOR: PROFESSOR N. ELDER
Department of Medical Microbiology
London School of Hygiene & Tropical Medicine

DATE: 26.3.84

CAUSAL PROPRIETARY TEST NO: 2624

COMPOUND: LON 1877 WR 199508 AD BOTTLE NO: BK 56500
 FORMULATION: Tween 80-H₂O ROUTE: sc/4776 TIME AFTER INFECTION: 7 HOURS
 HOST: ♂ PER mice PARASITE: P. yoelii mageriensis STRAIN: NIG

Dose	PATENCY RATE		OSP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-e)	Prophylactic activity (b-a)-(d-e)	
Ø	5/5	5/5	4.87 (d)	2.92 (d)				
30.0	3/3	3/3	4.91 (d)	2.96 (d)	0.04	0.04	NIL	INACTIVE
100.0	3/3	3/3	6.61 (d)	2.96 (d)	1.74	0.04	1.70	SLIGHTLY ACTIVE
			(d)	(d)				
			(d)	(d)				
			(d)	(d)				
			(d)	(d)				

SPOROZOITE ACTIVITY: > 100
 SPOROZOITE ACTIVITY: 100
 SPOROZOITE ACTIVITY: 100

CAUSAL PROPRIETARY TEST NO: 2624
 FORMULATION: Tween 80-H₂O
 HOST: ♂ PER mice

DATE: 20 1 55

CAUSAL PROPHYLAXIS TEST NO: 2465

COMPOUND: LON/ 1783 ANC - IX - 19

BOTTLE NO:

FORMULATION: Tween 80/H₂O

ROUTE: sc 47/40

TIME AFTER INJECTION: 2 HOURS

HOST: ♂ TFW mice

PARASITE: *P. yoelii nigeriensis*

STRAIN: NID

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	5/5		(a) 5 16	(c)				
60.0	3/3		(b) 4 95	(d)	0	NIL	NIL	INACTIVE
100.0	3/3		(b) 4 49	(d)	0	NIL	NIL	INACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

TABLE

MINIMUM FULLY ACTIVE DOSEmg/kg
 RESIDUAL ACTIVITY: NIL
 PRESENT AT 100.0
 MARFID ATmg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 13.2.84

CAUSAL PROPHYLAXIS TEST NO: 2542

COMPOUND: LON/ 1908 3-bromo-phenazine diphenylate BOTTLE NO: RCGJM 97

FORMULATION: Tween 80/H₂O

ROUTE: sc/it/ho TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice

PARASITE: P. yoelii nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2 nd P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (a)	Sporozoite and blood infected (c)	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	5/5	5/5	5.89 (a)	3.35 (c)	0	0	0	INACTIVE
10.0	3/3	3/3	4.88 (b)	3.17 (d)	0	0	0	SLIGHT RESIDUAL ACTIVITY ONLY
30.0	3/3	3/3	5.79 (b)	4.14 (d)	0	0.79	0	FULLY ACTIVE - SOME RESIDUAL ACTIVITY
100.0	0/3	3/3	>14.00 (b)	5.18 (d)	>8.11	1.83	>6.28	

MINIMUM FULLY ACTIVE DOSE 30.0 mg/kg

RESIDUAL ACTIVITY: PRESENT AT 30.0 mg/kg

MARSHED AT

PRINCIPAL INVESTIGATOR: PROFESSOR W. L. L. L.
Department of Medical Microbiology
London School of Hygiene & Tropical Medicine

DATE: 19 3 84

CAUSAL PROPHYLAXIS TEST NO: 2608

COMPOUND: LON/ 1884 Ph 4007

BOTTLE NO: BK 64306

FORMULATION: Tween 80/H₂O ROUTE: sc/4474 TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TEW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		CMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	5/5	4.87 (a)	3.86 (c)				
100.0	3/3	3/3	4.93 (b)	3.57 (d)	0.06	0	NIL	INACTIVE
300.0	1/3	3/3	> 11.61 (b)	3.62 (d)	> 6.74	0	> 6.74	ACTIVE

TABLE 25

MINIMUM FULLY ACTIVE DOSE > 300mg/kg
 RESIDUAL ACTIVITY: NIL ~~300~~ AT 300mg/kg
 MARKED ATmg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 2608
 COMPOUND: LON/ 1885
 FORMULATION: Tween 80/H₂O
 HOST: ♂ TFW mice

DATE: 19. 3. 84
 BOTTLE NO: BK 64315
 ROUTE: sc/47/40
 TIME AFTER INFECTION: 2 HOURS
 STRAIN: NIG

PARASITE: *P. yoelii nigeriensis*

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	5/5	4/87 (a)	3/86 (c)				
100.0	3/3	3/3	5/42 (b)	3/54 (d)	0.55	0	0.55	INACTIVE
300.0	3/3	3/3	5/40 (b)	3/54 (d)	0.53	0	0.53	INACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

TABLE 29

MINIMUM FULLY ACTIVE DOSEmg/kg
 RESIDUAL ACTIVITY: NIL
~~PRESENT~~ AT 300mg/kg
 MARKED ATmg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. FLERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 19.3.84

CAUSAL PROPHYLAXIS TEST NO: 2608

BOTTLE NO: BK 64324

Ph 4900

TIME AFTER INFECTION: 2 HOURS

ROUTE: sc/44/44

STRAIN: NIG

PARASITE: *P. yoelii nigeriensis*

COMPOUND: LON/ 1886

FORMULATION: Tween 80/H₂O

HOST: ♂ TFW mice

DOSE mgm/kg	PATENCY RATE		GNP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (a)	Sporozoite and blood infected (c)	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	5/5	4.87	3.86				
100.0	3/3	3/3	5.12	3.53	0.25	0	NIL	INACTIVE
300.0	3/3	3/3	4.92	3.58	0.05	0	NIL	INACTIVE

TABLE 39

MINIMUM FULLY ACTIVE DOSEmg/kg
RESIDUAL ACTIVITY: NIL
PRESENT AT300.....mg/kg
MARKED ATmg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 26008

DATE: 19 3 84

COMPOUND: LON/ 1887 Ph 4901

BOTTLE NO: BK 64333

FORMULATION: Tween 80/H₂O

TIME AFTER INFECTION: 7 HOURS

HOST: ♂ TFW mice

PARASITE: E. poellii nigricans

STRAIN: N10

DOSE mg/kg	PATENCY RATE		GMP 27 P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (d)	Sporozoite and blood infected (d)	Total activity (b-a)	Residual activity (d-b)	Prophylactic activity (b-a)-(d-b)	
0	5/5	5/5	481 (d)	380 (d)				
100.0	3/3	3/3	685 (d)	380 (d)	1.98	0	1.98	SLIGHTLY ACTIVE
300.0	2/3	3/3	> 888 (d)	380 (d)	> 3.99	0	> 3.99	ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

Table 31

MINIMUM FULLY ACTIVE DOSE 300 mg/kg

RESIDUAL ACTIVITY: NIL

AT 300 mg/kg

MARFED AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 13.2.84

CASAL PREPARATION: 2542

BOTTLE NO: BK 51630

COMPOUND: LON 1872 WR 250547 AA

FORMULATION: Tween 80/H₂O ROUTE: sc/ ~~ip~~ TIME AFTER INFECTION: 2 HOURS

host: 3 IFM mice PARASITE: *P. yoelii nigeriensis* STRAIN: NIG

Dose mg/kg	PATENCY RATE		GMP 27 P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0.5	5/5	5/5	5.89 (b)	3.35 (c)				
0.1	3/3	3/3	5.13 (b)	3.48 (d)	0	0.13	NIL	INACTIVE
0.3	3/3	3/3	5.69 (b)	4.06 (d)	0	0.71	NIL	RESIDUAL ACTIVITY ONLY
1.0	3/3	3/3	7.36 (b)	5.69 (d)	1.47	2.34	NIL	RESIDUAL ACTIVITY ONLY
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

TABLE 1

PRIMUM FULLY ACTIVE DOSEmg/kg
RESIDUAL ACTIVITY: ~~+++~~
PRESENT AT 0.3mg/kg
MARKED ATmg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. L. F. F.
Department of Medical Zoology
London School of Hygiene & Tropical Medicine

DATE: 19 6 84

CAUSAL PROPHYLAXIS TEST NO: 2821

COMPOUND: LON/ 1941 Spiramycin

FORMULATION: Tween 80/H₂O

HOST: ♂ TFW mice

PARASITE: *P. yoelii nigeriensis*

ROUTE: s.c./i.p.

STRAIN: NIG

TIME AFTER INFECTION: 2 HOURS

STRAIN: NIG

BOTTLE NO:

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	3/3		(a) 5.46	(c)				
30.0	2/3		(b) > 9.75	(d)	> 4.29			ACTIVE
100.0	0/3 *		(b) > 14.00	(d)	> 8.54			FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MAXIMUM FULLY ACTIVE DOSE 30.0 mg/kg
 RESIDUAL ACTIVITY: ALL PRESENT AT mg/kg
 MARKED AT mg/kg

* 1/3 USED

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 19.6.84

CAUSAL PROPHYLAXIS TEST NO: 2821

COMPOUND: LON/ 1944 *Lincomycin hydrochloride* BOTTLE NO:

FORMULATION: Tween 80/H₂O ROUTE: sc/4p/100 TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: *P. yoelii nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	3/3		(a) 5.46	(c)				
30.0	2/3 *		(b) 6.87	(d)	1.41			SIGHTLY ACTIVE
100.0	1/3		(b) > 11.65	(d)	> 6.19			ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

TABLE 3

MINIMUM FULLY ACTIVE DOSE > 100 mg/kg

RESIDUAL ACTIVITY: NIL

PRESENT AT

MARFED AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

5.3 GAMETOCYTOCIDAL TEST DATA

30,

30,

30,

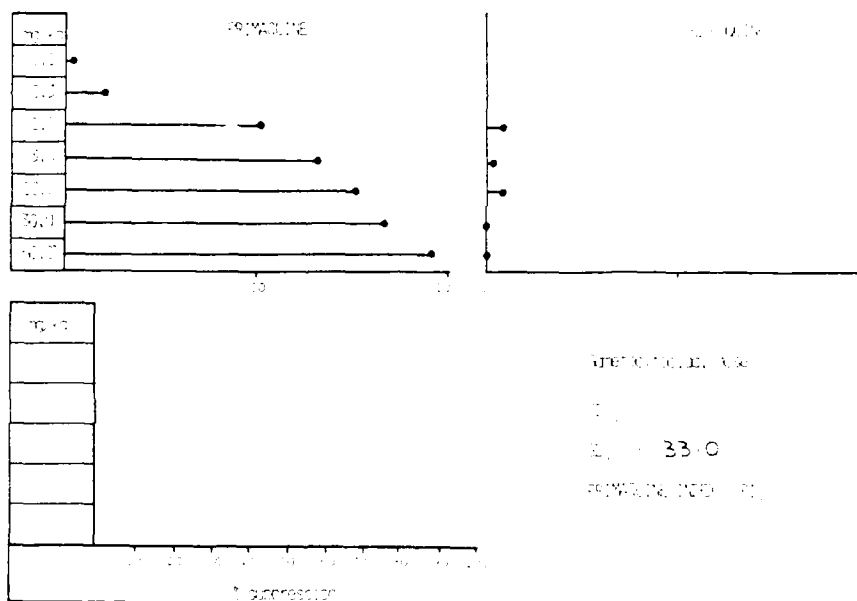
FILE : _____

OFFICE NO. 2373 JAN 23 1933

OFFICE NO. 2373 JAN 23 1933

NUMBER OF **ADULTS** **PER** **SAMPLE**

DOSE mg/kg	DOSE-RESPONSE										100	1000
2	45	16	13	14	13	3	21	10	48	16	17.8	10
	15	11										
1.0	13	3	10	8	3	6	4	7	13	20	8.7	48.9 ± 3.3
3.0	8	5	6	7	5	2	2	3	18	5	6.1	34.2 ± 3.9
10.0	2	1	4	6	5	5	2	8	9	1	4.3	24.2 ± 4.3
30.0	1		1	6	3	4	7	3		2	2.9	6.8 ± 3.4
60.0	0	0	2	1	1		2	0	0	0	0.4	1.0 ± 1.0



• **• • • • •**

2010年12月15日 星期三

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3.6

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LON 1720 WR 182234 BE 17580

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / ~~IP~~ / ~~IV~~ / ~~IM~~

MAXIMUM FULLY TOLERATED DOSE : > 100 mg / kg X 1

EXPERIMENT No.: 2422

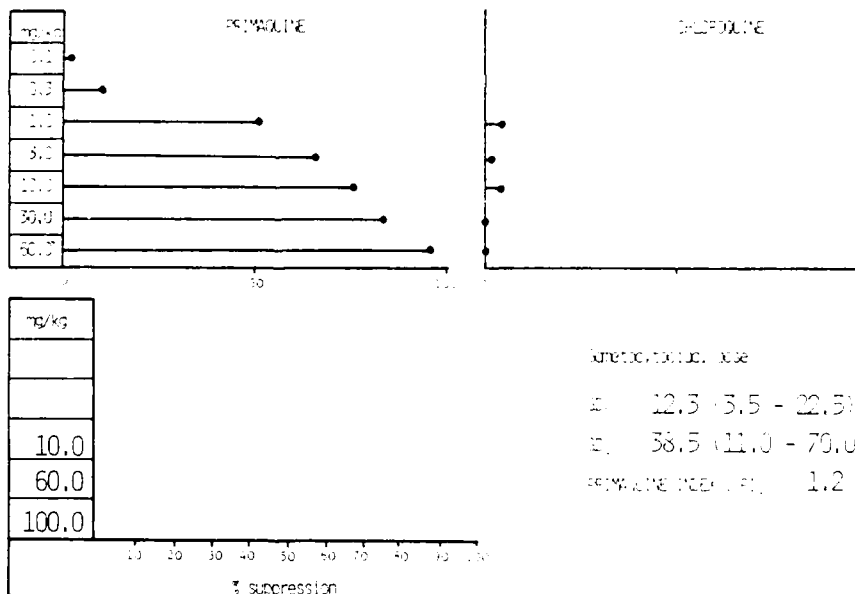
DATE : 7.12.83

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS 0+7										MEAN	% CONTROL
0	15	16	12	7	16	11	14	16	18	10	14.0	100
	16	14	19	16	10							
10.0	7	4	8	4	8	5	8	6	4	10	6.4	45.7 ± 4.3
60.0	4	3	0	1	0	1	3	2	2	1	1.7	12.0 ± 2.9
100.0	0	0	1	2	0	2	1	0	0	1	0.7	0.5 ± 0.5



Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3

GAMETOCYCIDAL ACTIVITY

COMPOUND : LON 1721 WR 211814 ZP 12775

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / ~~49-50-51-52~~

MAXIMUM FULLY TOLERATED DOSE : >100 mg / kg X 1

EXPERIMENT No.: 2422

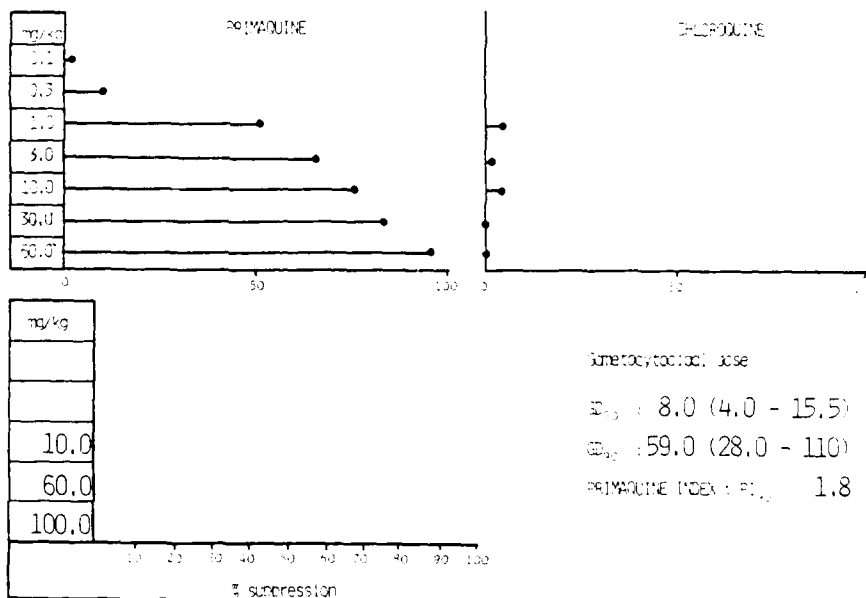
DATE 7.12.85

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : 5⁺ FEM MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS D+7										MEAN	% CONTROL	
2	15	16	12	7	16	11	14	16	18	10	14.0	100	
	16	14	19	16	10								
10.0	8	0	0	6	5	4	5	9	5	6	4.8	34.3	6.4
60.0	7	2	1	2	0	3	1	3	1	0	2.0	14.3	5.0
100.0	2	1	2	1	2	0	0	0	1	0	0.75	5.4	1.4
	0	0											



Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3/5

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LW 1722

WR 215295

ZN 43444

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / ~~IP~~ ~~PO~~ ~~IV~~

MAXIMUM FULLY TOLERATED DOSE : > 300 mg / kg X 1

EXPERIMENT No. : 2422

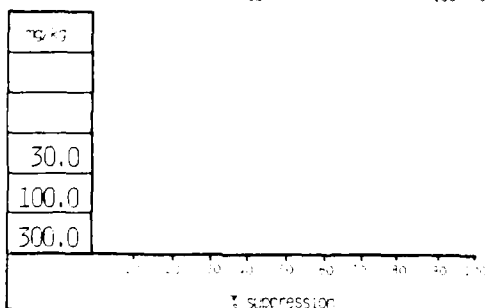
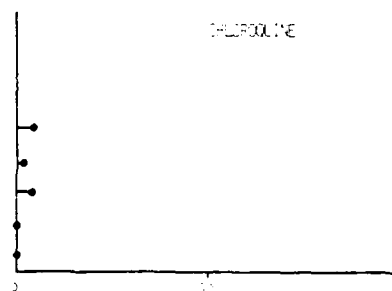
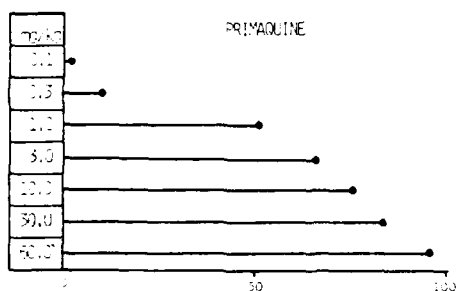
DATE : 7.12.83

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	GOCYST COUNTS D+7										MEAN	% DEATH
0	15	16	12	7	16	11	14	16	18	10	14.0	100
	16	14	19	16	10							
30.0						From Experiment 2151						96.8
100.0	14	13	14	8	9	8	7	13	15	6	9.9	70.7 ± 6.4
300.0	8	9	6	7	3	9	5	5	7	6	6.5	46.4 ± 4.3



Gametocytocidal dose

ED₅₀ : 230 (160 - 330)

ED₉₀ : 1100 (740 - 1500)

PRIMAQUINE INDEX : FI₅₀ 33.3

Principal Investigator : Professor W. Peters

Department of Medical Parasitology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3.9

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LQX 1727

WR 238605

BH 69990

FORMULATION : TWEEN 80 / H₂OROUTE : SC / ~~IP~~ / ~~PO~~ / ~~IV~~

MAXIMUM FULLY TOLERATED DOSE : >300 mg/kg x 1

EXPERIMENT NO.: 2453

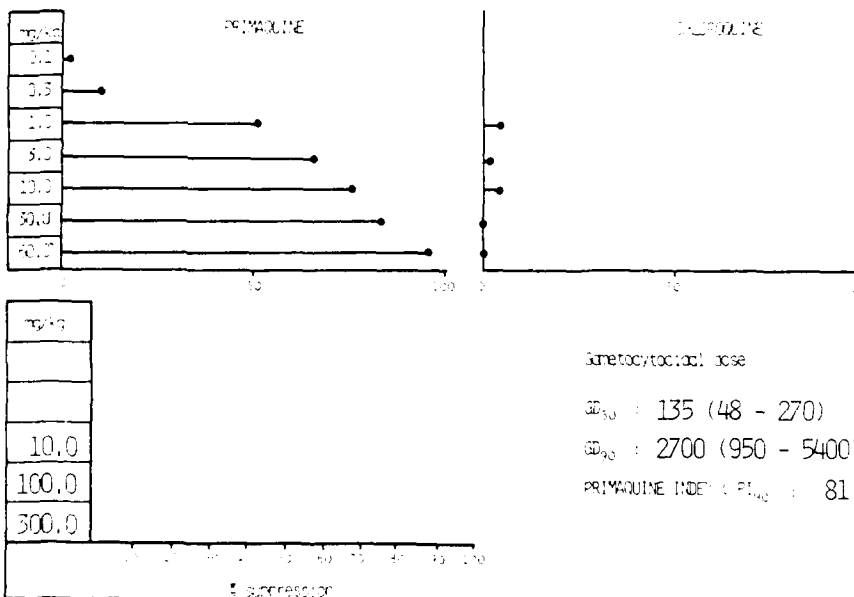
DATE 11.1.84

PARASITE : *Plasmodium yoelii* yoelii

VERTEBRATE HOST : ♂ IFN MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS D+7										MEAN	% CONTROL
0	47	73	38	35	20	38	30	28	29	16	33.5	100
15												
10.0	20	36	28	30	22	31	28	50	37	22	30.4	90.7 ± 4.0
100.0	19	14	7	27	23	2	20	17	14	23	16.0	47.8 ± 7.5
	12	14										
300.0	10	16	16	20	20	11	12	16	21	15	14.7	43.9 ± 3.5



Principal Investigator : Professor A. Peters


Co-investigator : Medical Entomology

Principal Investigator : Professor A. Peters

Page 10

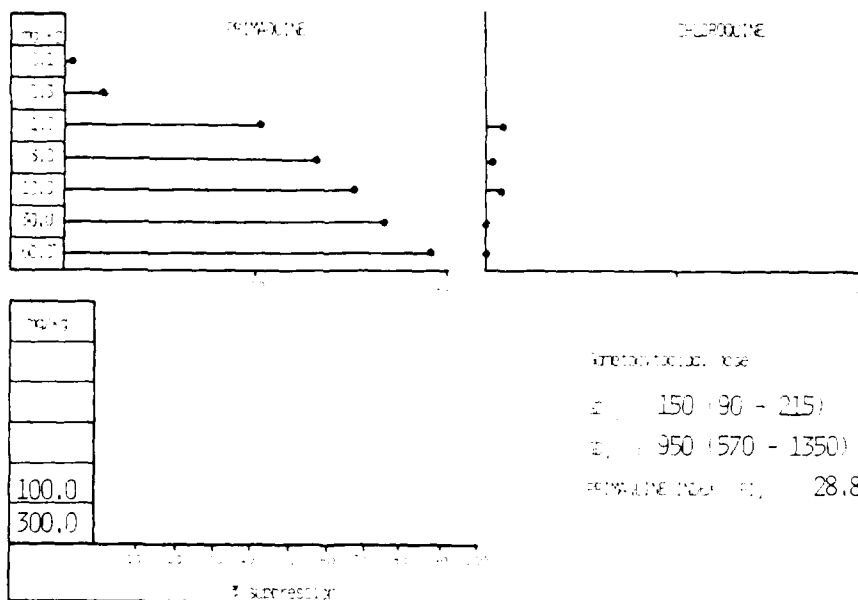
Page 10

BJ08189

ROUTE : SC 

EXPERIMENT No.: 2453

DATE: 11.1.84

INVERTEBRATE HOST: *Anopheles stephensi*.[illegible]

59

SUMMARY OF ANTIMALARIAL TESTS

TABLE 11

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LON 1729

WR 246315

BJ 45691

FORMULATION : TWEEN 80 / H₂OROUTE : SC / ~~IP / PO / IV~~

MAXIMUM FULLY TOLERATED DOSE : > 300 mg / kg X 1

EXPERIMENT No.: 2453

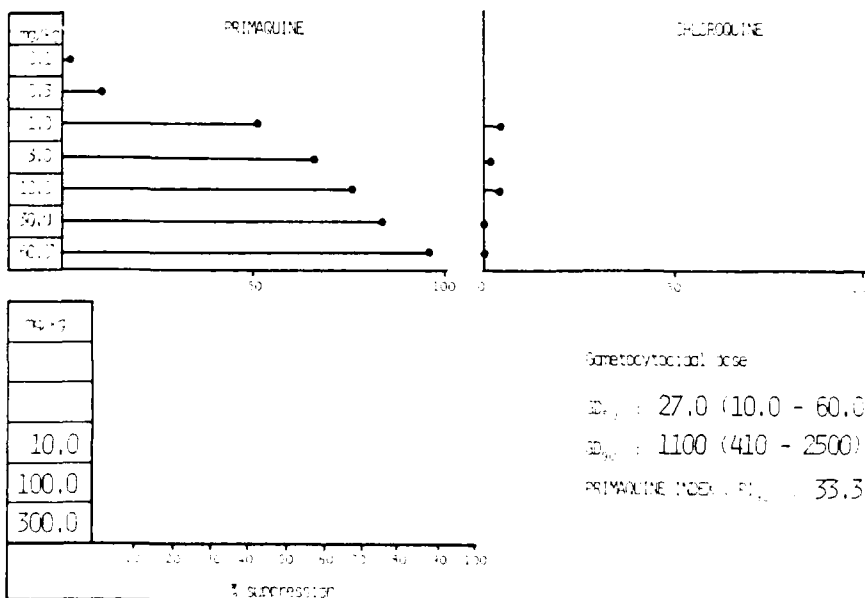
DATE : 11.1.84

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ TFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS 0+7										MEAN	% CONTROL
a	47	73	38	35	20	38	30	28	29	16	33.5	100
	15											
10.0	18	26	24	12	20	18	33	18	21	28	22.5	67.0 ± 6.3
	29											
100.0	16	12	18	14	17	10	17	12	19	8	13.6	40.7 ± 3.6
	7											
300.0	5	13	6	4	5	2	12	13	9	12	7.8	23.4 ± 3.3



Principal Investigator : Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 12

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LW 1730 WR 247705 BJ 51779

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / ~~IP~~ ~~IV~~

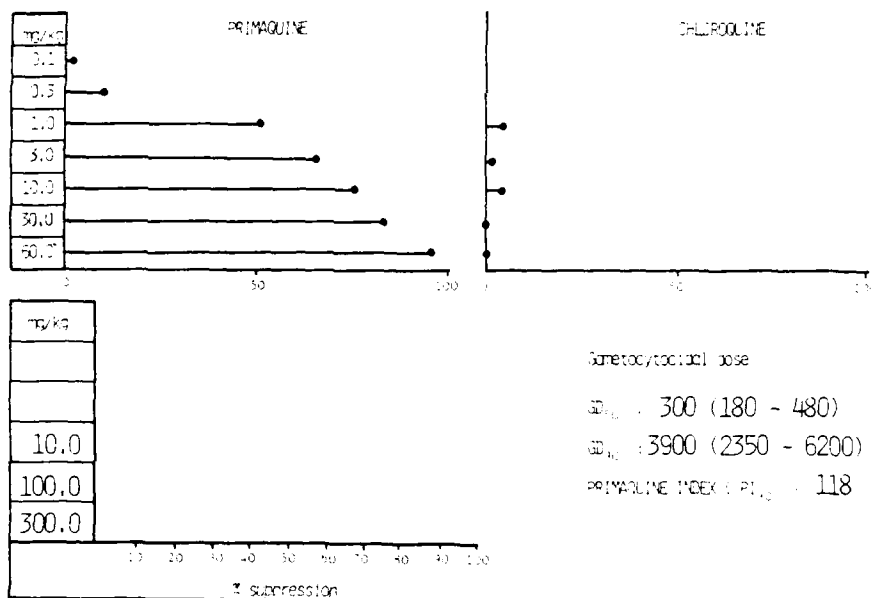
MAXIMUM FULLY TOLERATED DOSE : >300 mg / kg X 1 EXPERIMENT No.: 2501 DATE : 1.2.84

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ TFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS D+7										MEAN	% CONTROL
a	29	10	28	20	11	24	22	17	30	10	21.1	100
	10											
10.0	22	19	20	12	16	20	17	18	13	17	16.7	79.1 ± 4.3
	14	12										
100.0	17	23	13	18	9	27	17	21	6	0	15.1	71.6 ± 10.0
300.0	19	6	9	12	11	14	7	9	13	5	10.5	49.8 ± 6.6



Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 4.3

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LUN 1731

WR 248412

BJ 59202

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / IP / PO / IV

MAXIMUM FULLY TOLERATED DOSE : > 300 mg / kg X 1

EXPERIMENT No. : 2501

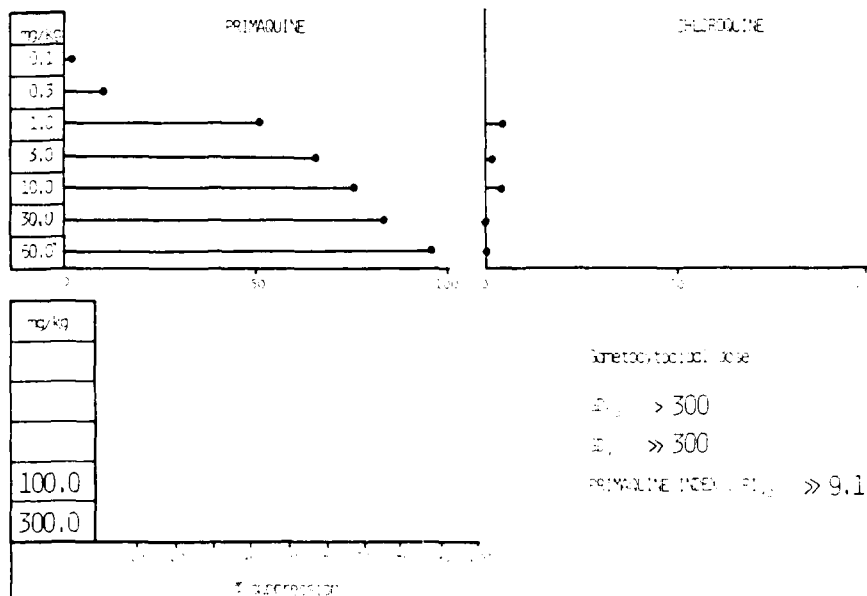
DATE : 1.2.84

PARASITE : *Plasmodium yoelii* nipertensis

VERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	DOCYST COUNTS D+7										MEAN	% CONTROL
0	29	10	28	20	11	24	22	17	30	10	21.1	100
	10											
100.0	21	13	13	17	20	18	12	16	10	18	16.0	75.8 ± 5.2
	18											
300.0	19	17	25	18	20	16	18	3	8	18	15.3	72.4 ± 8.6
	6											



Principal Investigator : Professor W. Petent
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

1997

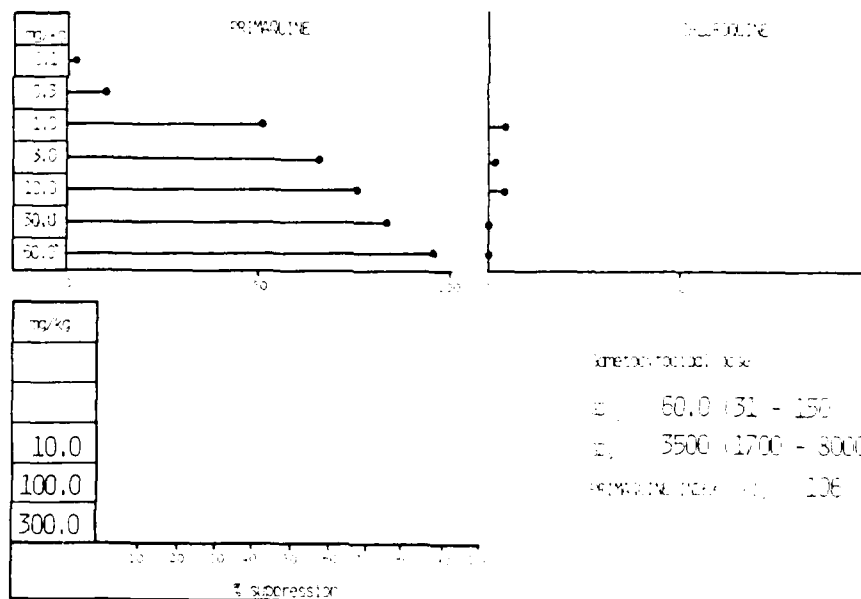
BH 58120

Figure 1. \rightarrow 1,2,3,4,6-pentakisubstituted pyranose

EXEMPTED 2501

42 1.2.84

INVERTEBRATE HOST : *Artemes hercules*.

[illegible]

Principal Investigator - Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANIMAL EXPERIMENTAL TESTS

TABLE 1.1

ANETHROCYCLOL ACETATE

MEMO: LIA 1733 NR 228708 BG 60798

ANESTHESIA TAKEN > 1 mg/kg ROUTE: i.p. - 100% - 100%

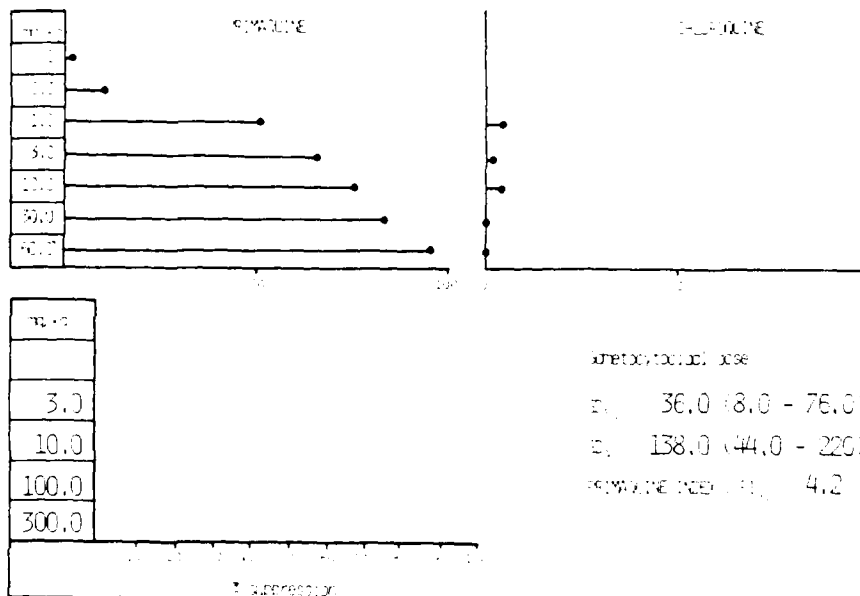
MAXIMUM TOLERATED DOSE > 300 mg/kg i.p. EXPERIMENT NO: 2519 DATE: 8.2.84

PARASITE: Plasmodium falciparum

INVERTEBRATE HOST: A. TA. MUI

INVERTEBRATE HOST: Agoutis stephens

DOSE mg/kg	DOSEY COUNTS 0-7										MEAN	STANDARD	
1	15	12	18	16	18	14	17	16	18	18	16.5	1.1	
	19												
3.0	27	22	12	14	14	20	19	19	16	18	18.1	100	1.5
10.0	12	9	8	7	10	11	3	6	10		8.4	50.3	5.5
100.0	7	7	6	0	5	0	0	7	5	0	3.7	22.4	4.2
300.0	3	0	0	0	5	2	0	0	0	1	1.7	10.3	5.5



Principal Investigator: Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

Summary of Antimalarial Tests

Methodological Details

Formulation: LA 1751 WR 194343 ZN 41368

Formulation: Tween 80 Route: i.p. 40-45°C

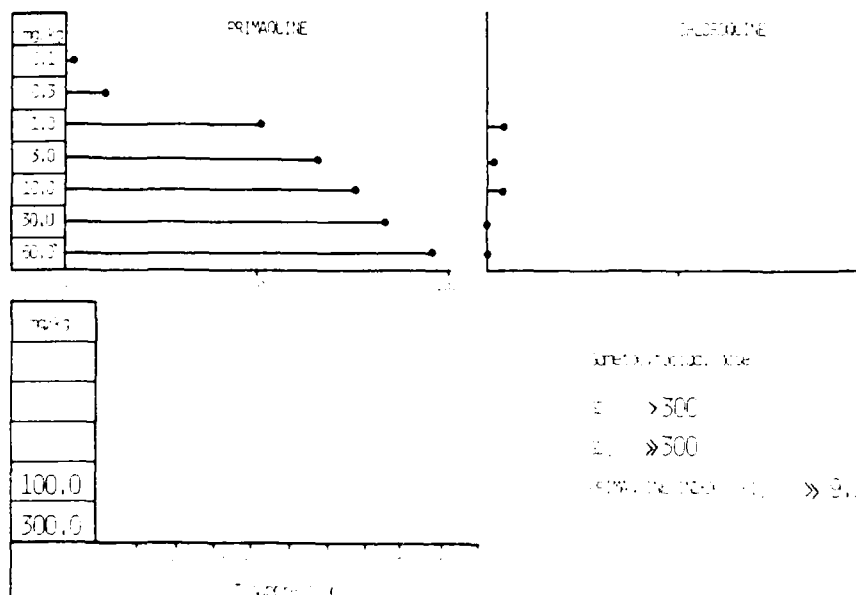
Maximum Fully Tolerated Dose: >300 mg/kg Experiment No: 2532 Date: 15.2.84

Parasite: *Plasmodium yoelii* (Yonderberg)

Intermediate Host: 2-3 Week Old

Intermediate Host: Anopheles (Stephensi)

Dose (mg/kg)	Sucklet Counts (0-7)										Mean	1 Control
2	18	27	48	10	11	17	12	11	21	14	18.0	19
	9											
100.0	16	15	7	8	19	12	18	8	13	25	13.5	75.0 ± 6.1
300.0	7	10	8	16	17	14	22	7	10	9	12.0	66.6 ± 6.1



Formulation: Primaquine (100.0 mg/kg)

Formulation: Chloroquine (100.0 mg/kg)

Formulation: Chloroquine (300.0 mg/kg)

SUMMARY OF ANTIMALARIAL TESTS

TABLE 4.7

DACTEOCYTICidal ACTIVITY

Compound: LW1783 ANC-IX-19 (McChesney) - WR 249725

Formulation: Tween 80 / H₂O

Route: i.p. / i.p. / i.p.

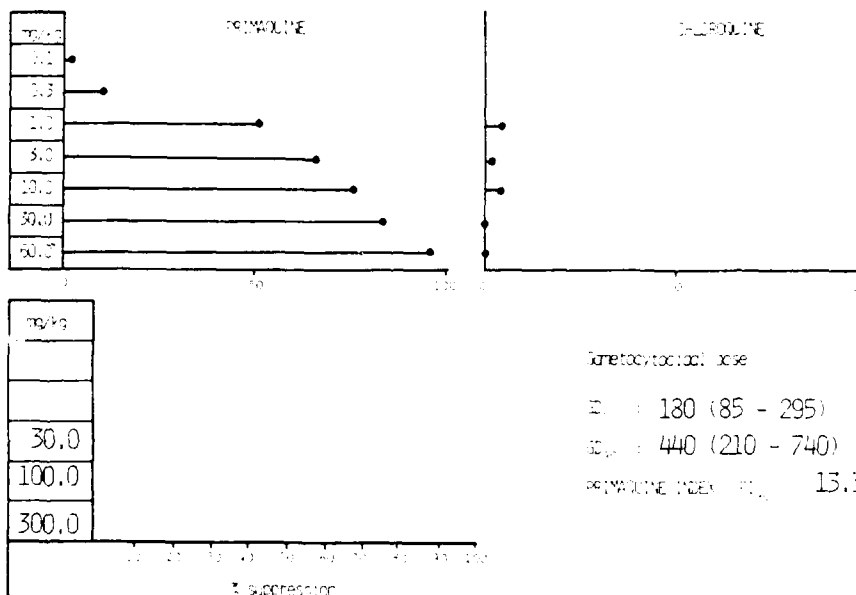
Maximum Fully Tolerated Dose: >300 mg/kg x 1 Experiment No. 2481 Date: 25.1.84

Parasite: *Plasmodium yoelii* (Nederlands)

Vertebrate Host: J. TRA WICE

Invertebrate Host: *Anopheles stephensi*

Dose (mg/kg)	DOCT COUNTS 0-7										Mean	* Control
0	15	18	17	19	20	24	18	23	17	25	19.0	19.0
	14	12	23	21								
30.0	21	25	20	27	26	14	25	18	8	15	19.9	100 ± 10.0
100.0	5	14	13	3	1	10	13	14	9	14	9.6	50.5 ± 6.8
300.0	7	14	2	5	8	12	8	7	10	8	8.1	42.6 ± 6.3



Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 1-5

ANTI-TOXOPLASMA ACTIVITY

COMPOUND: LW 1801

WR 15031

AY 15653

FORMULATION: TWEEN 80 + H₂O

ROUTE: SC (400/0.1/0.1)

MAXIMUM TOLERATED DOSE: >300 mg/kg (1)

EXPERIMENT NO.: 2632

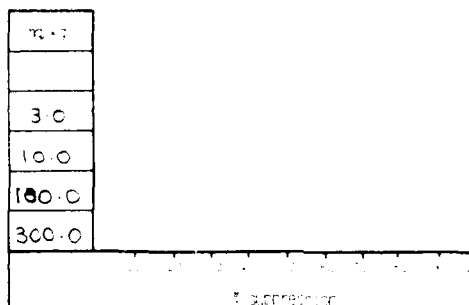
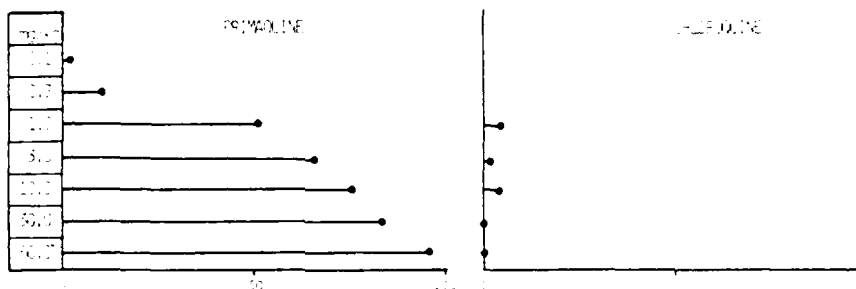
DATE: 4-4-64

PARASITE: *Plasmodium yoelii* nigeriensis

INTERMEDIATE HOST: 3 WEEK MICE

INTERMEDIATE HOST: *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS 3-7										MEAN	% CONTROL
0	11	39	14	22	16	24	15	14	13	33	20.1	100
3.0	15	5	20	12	13	11	22	21	12	21	15.2	75.6 ± 7.5
10.0	25	10	16	18	10	9	14	12			14.3	70.9 ± 6.8
100.0	11	7	12	19	22	13	28	12	8	18	15.0	74.6 ± 6.5
300.0	7	11	17	12	17	16	21	14			14.4	71.5 ± 9.1



Intermediary host

0 > 300

100 > 300

PRIMAQUINE DOSE: 300 > 9.1

Principal Investigator: Professor W. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

PAGE 1/1

ANTI-PROLIFERATIVE ACTIVITY

IMPACT: 1802

WR 6890

BK 12713

FORMULATION: 100% H₂O

ROUTE: 100% H₂O

MAXIMUM TOLERATED DOSE: > 300

EXPERIMENT NO.: 2560

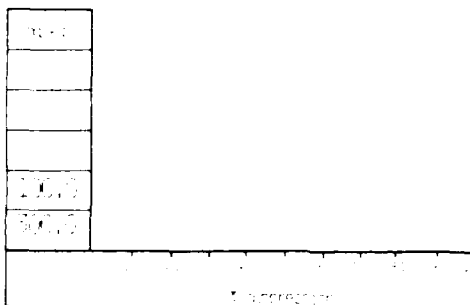
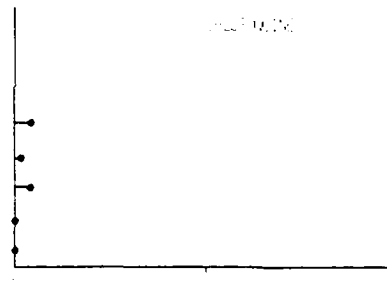
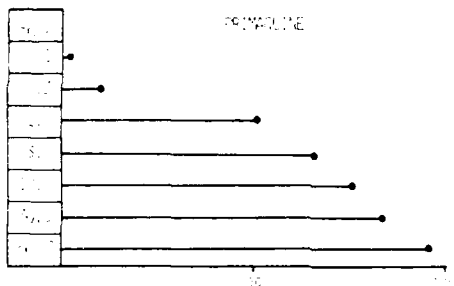
DATE: 29.2.84

PASASITE: *Plasmodium falciparum* (F3D7)

TESTERATE HOST: 100% H₂O

TESTERATE HOST: 100% H₂O

DOSE (mg)	DOSE COUNTS (n)											MEAN	ST. DEV.
0	30	33	29	39	17	18	30	24	20	17	25.7	1.1	
100.0	8	9	16	10	13	20	13	10	15	17	13.1	51.0 ± 2.3	
300.0	6	2	2	1	7	2	3	1	2	5	3.1	12.1 ± 1.4	



ANTIPROLIFERATIVE DOSE

100(90 - 110)

340(290 - 370)

PRIMAQUINE NEED: 10.3

Principal Investigator: Dr. Antonio M. Petroni

Co-Investigator: Dr. Antonio M. Petroni

Principal Investigator: Dr. Antonio M. Petroni

• 4500

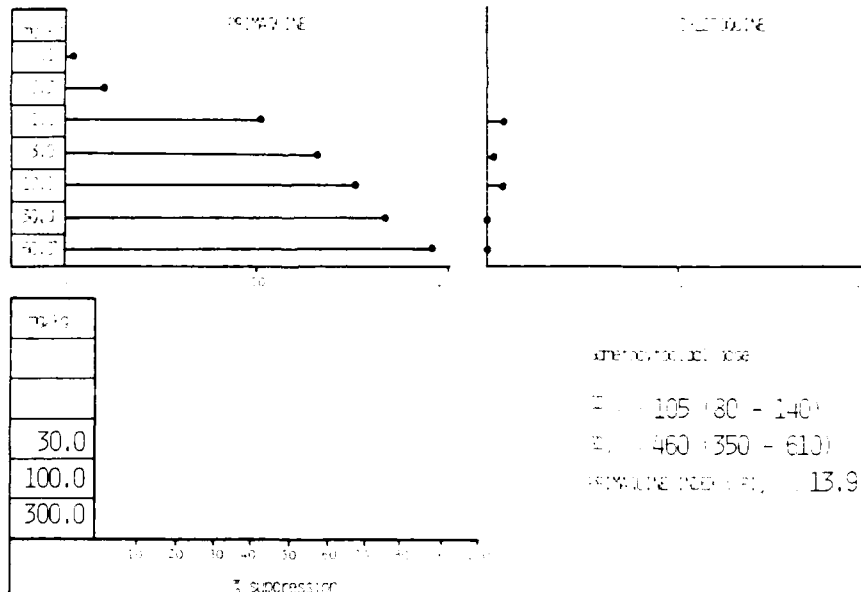
FORMULATION : TWEEN 80 / H₂O

ROUTE : 20 / 42 → 46 → 49

PARASITE : Plasmodium yoelii nigeriensis

VERTEBRATE HOST : ♂ FWH MICE

INVERTEBRATE HOST : Anomelies sternalis.

[illegible]

Principal Investigator : Professor W. Peters
Department of Medical Protozoology,
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TEST

Table 5.1

ANTHELMINTHIC ACTIVITY

Compound: LON 1877 MR 199508 AD BK 56500

Formulation: Tween 80/NaCl

Route: ~~SC~~ ~~IP~~ ~~IV~~ ~~IT~~ ~~IT~~ ~~IT~~

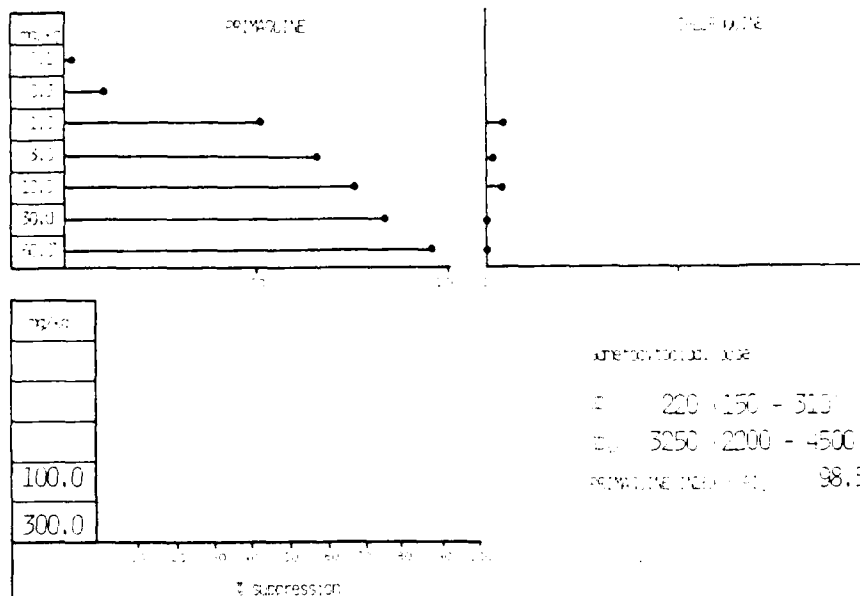
Maximum fully tolerated dose: >300 mg/kg (1) Experiment no: 2560 Date: 29.2.84

Parasite: *Plasmodium yoelii* *berghei* 1918

Vertebrate host: 3-4 week mice

Invertebrate host: *Aedes albopictus*

Dose mg/kg	DOCT COUNTS 3-7										Mean	Standard deviation
0	30	33	29	39	17	18	30	24	20	17	25.7	1.0
100.0	19	17	14	20	17	27	8	14	21	11	16.8	65.4 ± 6.9
300.0	17	6	16	10	13	10	15	12	11	9	11.9	46.3 ± 4.3



Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIPYRETIK TEST

Page 5/2

ANTIPYRETIK ACTIVITY

Compound: LA 1931 WR 249725 BK 69990

Formulation: Tween 80 + H₂O Route: i.p. / 180000000

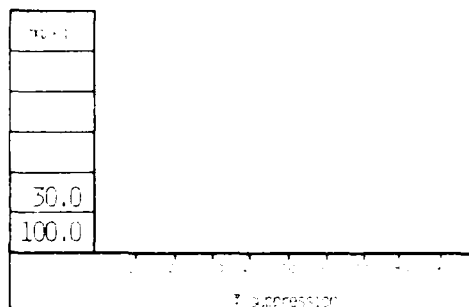
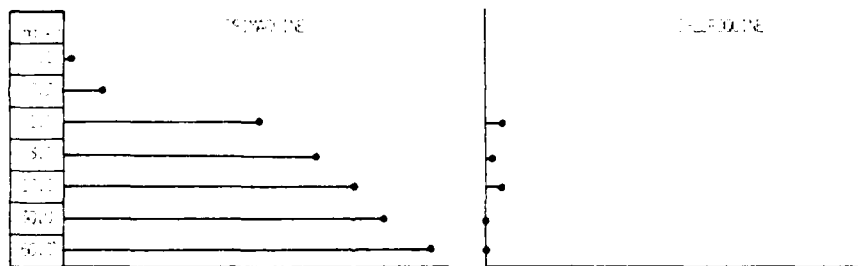
Maximum fully tolerated dose: >100 mg/kg Experiment No.: 2645 Date: 11.4.85

Parasite: Plasmodium falciparum

Febrile host: ♂ Fawn Mice

Nonfebrile host: Noninfected, febrile

Dose (mg/kg)	Log ₁₀ Counts ± s.e.										Mean	± Control
0	21	13	18	8	20	24	6	11	14	12	15.5	10
	23											
30.0	19	12	21	11	18	13	23	18	20	19	16.9	100 ± 2.9
	12											
100.0	22	14	18	11	16	20	14	13	19	8	15.5	100 ± 4.8



Antipyretic dose

1 >> 100

4 >> 100

Maximum tolerated dose >> 3.0

Principal Investigator: Professor W. Peters
Department of Medical Pharmacology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TEST

SLIDE 5-1

ANTI-PROTOZOAL ACTIVITY

MPHIC 1884 Ph 4007 BK 64306

FORMULATION: TABLETS

ROUTE: PO (48-48-48-48)

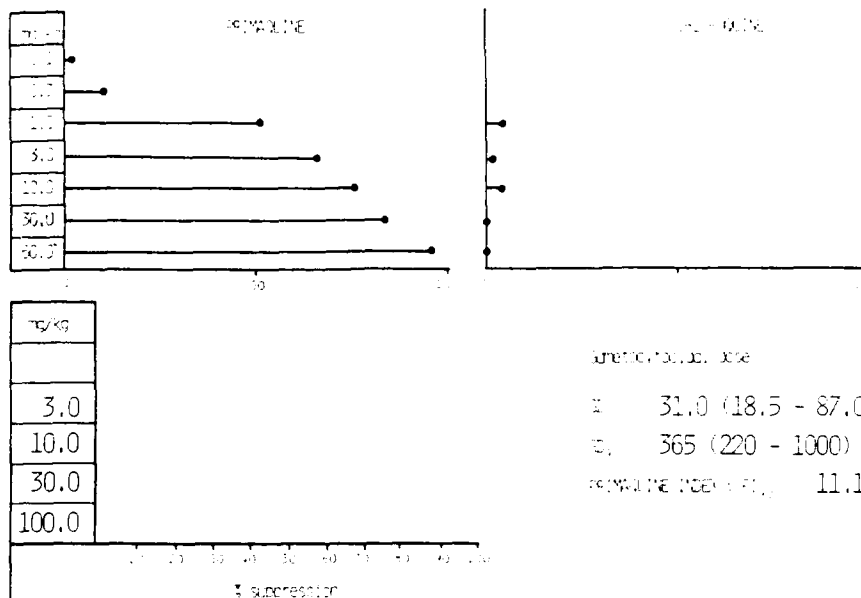
MAXIMUM FULLY TOLERATED DOSE: >100mg/kg/day EXPERIMENT NO. 2589 DATE: 14.3.84

PARASITE: Plasmodium falciparum

INVERTEBRATE HOST: A. stephensi

INVERTEBRATE HOST: Anopheles stephensi

DOSE (mg/kg)	XOXYSTUARTS 1-7										MEAN	ST. DEV.
7	12	16	23	16	20	16	17	18	17	24	17.9	1.7
3.0	18	13	16	18	15	10	21	17	20	16	16.4	91.6 ± 4.4
10.0	13	22	15	15	8	11	14	7	12	15	13.2	73.7 ± 6.1
30.0	8	6	7	11	9	8	14	4	9	8	8.4	46.9 ± 5.8
100.0	7	0	3	9	7	5	9	8	4	0	5.8	32.4 ± 5.0



Principal Investigator: Professor W. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TEST

ANTHELMINTIC ACTIVITY

REFERENCE No. 1885

Ph 4017 BK 64315

FORMULATION: TWEEN 80 + H₂O

PURITY: 100% (estimated)

MAXIMUM FULLY TOLERATED DOSE: >100 mg/kg

EXPERIMENT No. 2589

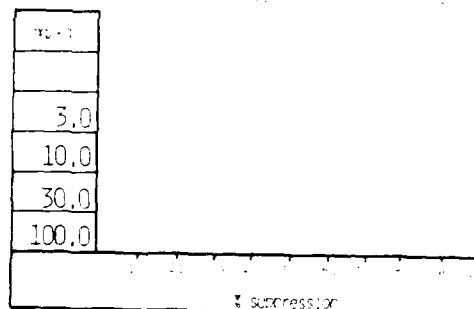
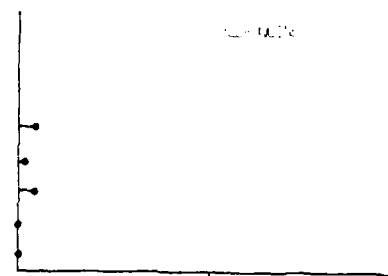
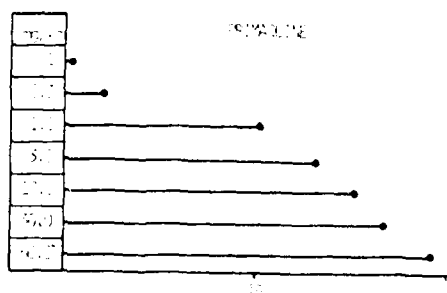
DATE: 14.3.84

PARASITE: *Plasmodium falciparum*

TESTER: H.C. J. DE WIT

INTERPRETER: H.C. J. DE WIT

DOSE (mg/kg)	DOCKET COUNTS (n=10)										MEAN	ST. DEV.
0	12	16	23	16	20	16	17	18	17	24	17.9	1.1
3.0	19	16	14	10	20	25	18	14	11	16	16.3	91.1 ± 4.4
10.0	13	16	14	18	21	15	16	11	14	10	14.8	82.7 ± 4.4
30.0	2	3	6	4	3	8	4	9	5	1	4.5	25.1 ± 4.5
100.0	4	2	5	0	4	3	0	3	6	6	3.3	18.4 ± 3.4



ANTHELMINTIC ACTIVITY

1. 20.0 (10.5 - 39.0)

2. 90.0 (47.0 - 175)

ANTHELMINTIC ACTIVITY: 2.7

Principal Investigator: Professor W. Peters

Department of Medical Parasitology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 5.71

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LW 1886

Ph 4900

BK 64324

FORMULATION : TWEEN 80 + H₂O

ROUTE : SC / TP / IP / IT / IT

MAXIMUM FULLY TOLERATED DOSE : >100 mg/kg x 1

EXPERIMENT No.: 2589

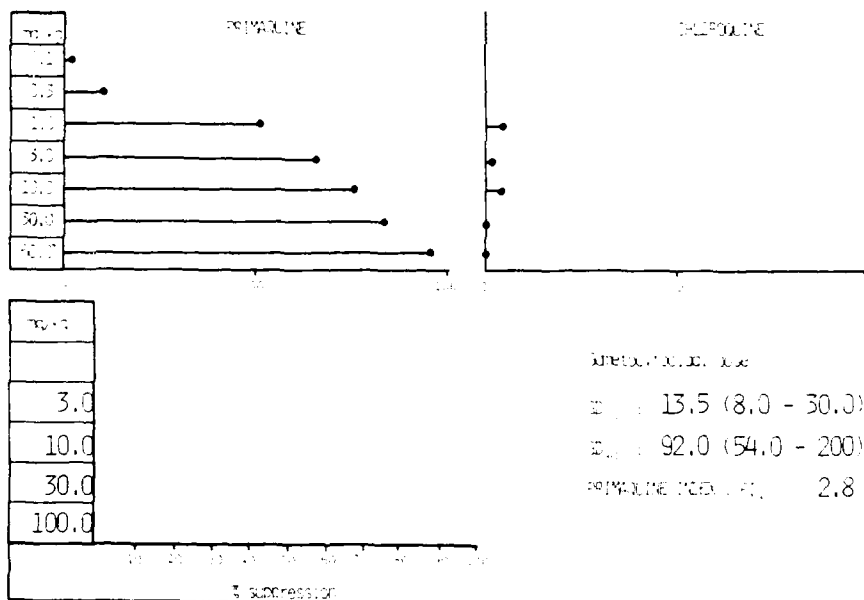
DATE : 14.3.84

PARASITE : *Plasmodium yoelii* nederlandsi

VERTEBRATE-HOST : ♀ TPA MICE

INVERTEBRATE-HOST : *Anopheles stephensi*

DOSE mg/kg	DOCYST COUNTS 0-7										MEAN	% CONTROL
0	12	16	23	16	20	16	17	18	17	24	17.9	100
3.0	14	13	16	20	10	28	11	22	9	18	16.1	89.0 ± 5.0
10.0	10	10	14	12	8	14	9	11	10	7	10.5	58.7 ± 3.9
30.0	4	1	2	3	6	4	3	6	5	8	4.2	23.5 ± 3.9
100.0	0	6	5	1	2	3	4	1	0	0	2.2	12.3 ± 3.4



Principal Investigator : Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 5 (1)

GAMETOCYCIDAL ACTIVITY

COMPOUND NAME 1887

Ph 4901

BK 64333

FORMULATION TWEEN 80 / H₂OROUTE : SC / ~~IP~~ ~~IV~~ ~~IM~~

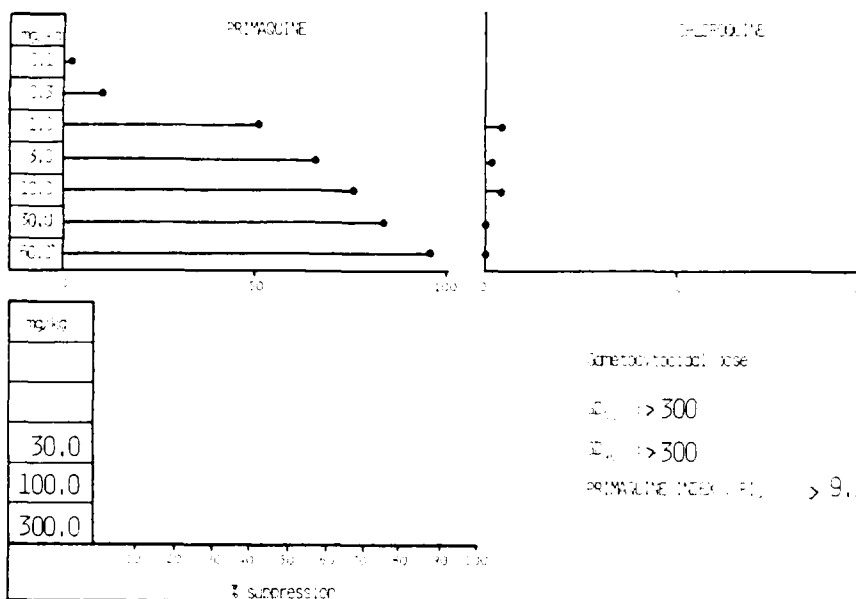
MAXIMUM TOLERATED DOSE : > 300 mg/kg x 1

EXPERIMENT No 2576

DATE 7.3.84

PARASITE *Plasmodium yoelii nigeriensis*VERTEBRATE HOST : δ^1 FWH MICEINVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	DOCT COUNTS D+7										MEAN	ST. DEV.
0	21	16	20	22	19	25	13	6	21		18.1	10
30.0	15	14	19	15	18	18	20	12	24	12	16.7	92.3 \pm 3.4
100.0	18	15	23	19	11	13	16	11	10	14	15.0	82.9 \pm 4.5
300.0	12	11	14	8	12	14	10	17	13	7	11.2	61.9 \pm 6.6
	5											



Principal Investigator : Professor W. Peters

Department of Medical Protozoology

London School of Hygiene & Tropical Medicine

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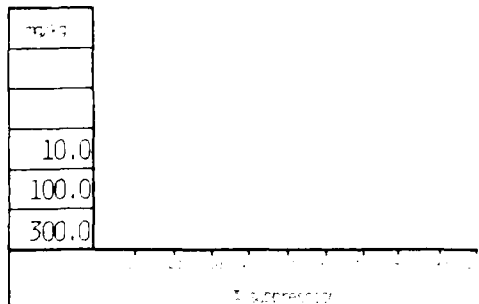
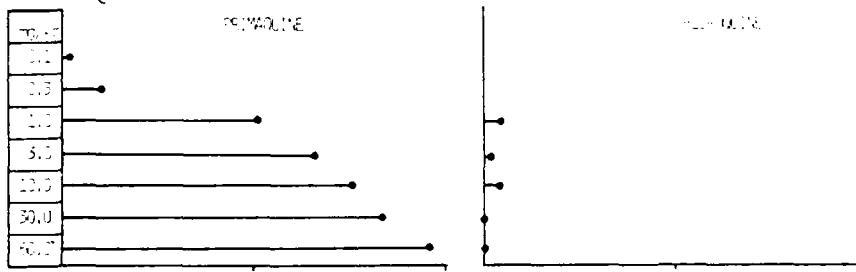
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IMPLOS - LG 1752 NR 245082 BK 02771

MAXIMUM ALLOWABLE DEGREE OF DEFLECTION > 300 mm (11.81 in) DISPLACEMENT 2532 mm (99.69 in) WIND 15.2.84

PARASITE : *Plasmodium falciparum* (Gerrard)

WESTERDALE, ALBERTA: Andrew Lesch, owner.

[illegible]

DE*U*U*U. 1x

$$= 70.0 - 28.0 = 42.0$$

2. 2100 (850 - 3500)

63.6

Principal Investigator: Professor A. Satero
Department of Medical Parasitology,
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TEST

DATE: 5/8

EXPERIMENTAL DESIGN

COMPOUND: 1753 WR 246976 BK 02780

FORMULATION: Tween 80 ROUTE: PO

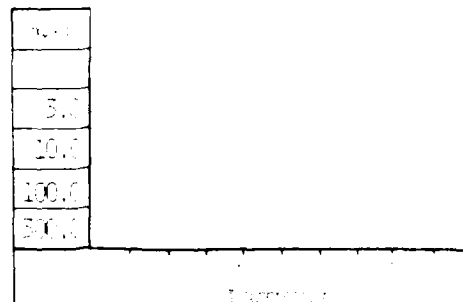
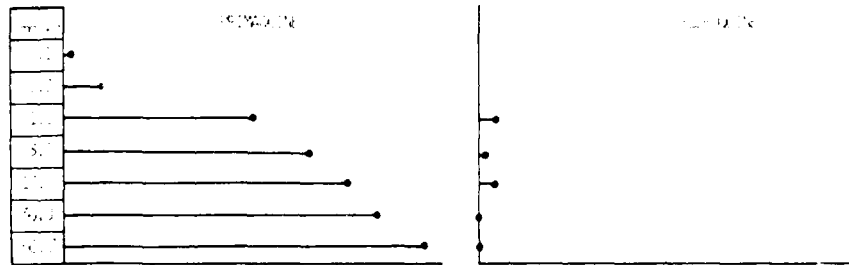
MAXIMUM FULLY TOLERATED DOSE: >300 mg/kg EXPERIMENT NO: 2532 DATE: 12/2/84

PARASITE: Plasmodium falciparum

TESTER: NOT SET YET

INTERPRETER: NOT SET YET

DOSE (mg/kg)	COUNT (NO. OF PARASITES)										MEAN	STANDARD DEVIATION
0	18	27	48	10	11	17	12	11	21	14	18.0	1.0
	9											
3.0	10	12	13	17	9	16	8	15	12	10	12.0	67.8 ± 5.1
10.0	11	18	11	6	12	4	8	15	10	14	11.0	90.4 ± 8.8
100.0	4	4	4	3	5	6	6	4	7		4.6	25.7 ± 1.7
300.0	2	1	3	1	2	0	1	1	2		1.3	7.2 ± 1.7



STATISTICAL ANALYSIS

1. 11.0 ± 5.1 ± 23.1

2. 25.7 ± 1.7 ± 51.7

3. 7.2 ± 1.7 ± 1.7

NOTE: The data are presented as mean ± standard deviation.

NOTE: The data are presented as mean ± standard deviation.

NOTE: The data are presented as mean ± standard deviation.

MEDICAL GROUP

FORMULATION: TWEEN 80 5.0

DATE: 10-1-84

PARASITE *Plasmodium falciparum* (Berl.)

REF ID: A61111

DEPT. OF AGRIC. ENG.

70.0
100.0
300.0

THEOREM 1.1. Let x

25-155-50

2000 1450 - 5010

1998, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 2679, 2680, 26

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Keywords: *Self-esteem; self-concept; self-identity; self-image*

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UNIVERSITY OF WISCONSIN

RECEIVED

INSTITUTIONAL ADDRESS

PHONE 1741 WS 102796 AD EC 78878

NAME AND ADDRESS OF

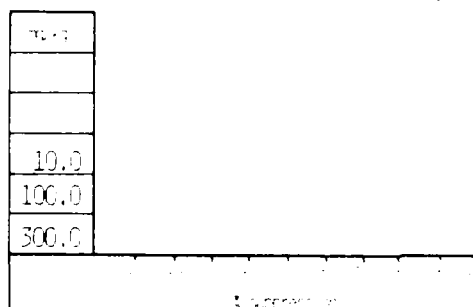
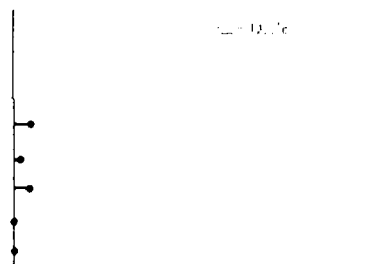
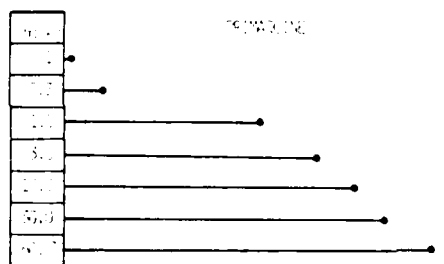
RESEARCH INSTITUTION >300 m 11 APPROXIMATE 2513

DATE OF STUDY

INSTITUTE FOR

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DOSE (mg)	DOSE (mg)										MEAN	ST. DEV.
2	15	12	18	16	18	14	17	16	13	18	10.5	
	19											
10.0	22	13	18	7	9	11	14	10	18	3	12.8	60.1 ± 5.5
	8											
100.0	16	3	5	9	10	6	0	6			0.4	42.8 ± 3.5
300.0	2	7	7	9	4	5	6	4	5	0	4.3	29.7 ± 5.5



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DATE OF STUDY

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INSTITUTE FOR

- 2 - 61

2007-05-01

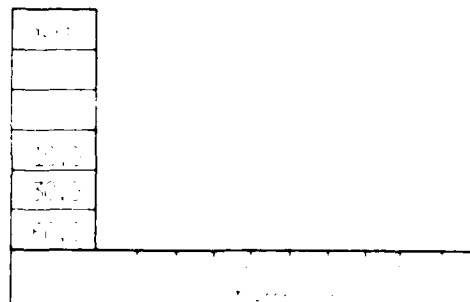
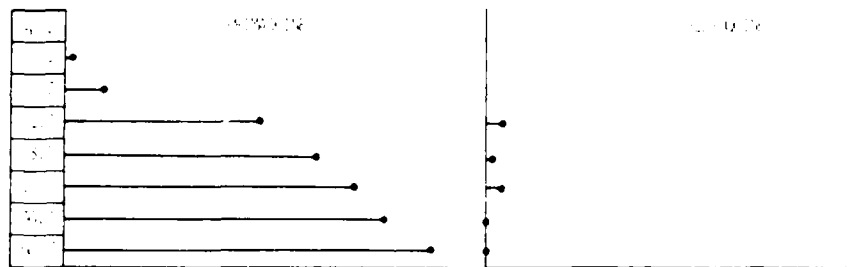
NAME: A-1100 WR 142490 BH 10371 Methylcodaine

FORM NO. 7-60 (Rev. 9-22-64) GPO : 1965 O - 384-484

ADDITIONAL COMMENTS: 100% ≥ 60 in 1991. REASON: 2481 WTS 15.1.84

4.4.1.1. General

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[illegible]

1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 26

11-40-240

100

 $\text{pH} = 1.8$

1. The first group of people who are not in the labor force are those who are not in the labor force for any reason. This group includes people who are not in the labor force because they are not in the labor force for any reason.

1. *Chlorophyll a* and *Chlorophyll b* were determined by the method of Arar and Collins (1971).

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

5.4 ORIENTATIONAL TEST DATA

PRIMARY PLASMODIUM TESTS

1012

TOXICOLOGICAL ACTIVITY

COMPOUND : LCN 1709 WR 225448 AG SH 58522

FORMULATION : DISSOLVED / SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS

PARASITE : *Plasmodium jelfi* (Copenhagen)

INVERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles gambiae*

TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ XXXX NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER : 2760

DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION (μg)	100-SP COUNTS (n = 7)										MEAN	STANDARD
2	15	26	14	73	92	77	77	22	34	36	55.3	1
0.05	36	44	25	23	29	27	40	23	37	20	32.4	34.2 ± 4.1

~~XXXXXXXXXXXXXXXXXXXX~~ INACTIVE AT 0.05 μg

EXTENDED TEST

CONCENTRATION (μg)	100-SP COUNTS (n = 7)										MEAN	STANDARD
2												1

0.05

	2	1	0.1	0.01	0.001	0.0001	0.00001	0.000001	0.0000001	0.00000001	0.000000001	0.0000000001
	μg/100 μl											

1. *Plasmodium jelfi* (Copenhagen) - 100-SP counts

2. *Anopheles gambiae* - 100-SP counts

3. *Plasmodium jelfi* (Copenhagen) - 100-SP counts

COMPARISON OF ANTIMALARIAL TESTS

Page 63

SPOROZOICIDAL ACTIVITY

COMPOUND : UN 1715 WR 5990 AG 99266

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : *Plasmodium yoelii* nipertensis

VERTEBRATE HOST : 3 FEM MICE

INVERTEBRATE HOST : *Anopheles gambiae*

TOXICITY : ~~XXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER : 2760

DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS (5 + 5)										MEAN	ST. CONTROL
2	15	26	14	73	32	37	17	22	34	38	35.6	
0.05	27	25	14	10	20	28	31	19	12	24	20.6	66.6 ± 6.9
	13											

~~XXXXXXXXXX~~ = ACTIVE ~~XXXXXXXXXX~~ = INACTIVE AT 100% T

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS (5 + 5)										MEAN	ST. CONTROL
2												

2
0.05

POTENTIAL Dose 100

100g

100g

100g 100g 100g 100g 100g 100g 100g 100g 100g 100g

0 suppression

Principal Investigator : Professor W. Peters

Department of Medical Microbiology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

14-10-84

POTENTIAL ACTIVITY

COMPOUND : JCN 1719 WR 181023 BE 50003

FORMULATION : DISSOLVED / SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : Plasmodium yoelii nigeriensis

VERTEBRATE HOST : 3 FEMALE MICE

INVERTEBRATE HOST : Anopheles stephensi

TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER : 2760

DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS (D + 7)										MEAN	T. ATROL.
3	15	26	14	73	32	37	17	22	34	38	35.8	34
0.15	25	20	30	16	29	15	23	18	25	21	21.8	60.9 ± 4.1

~~XXXXXXXXXXXX~~ SLIGHTLY ACTIVE ~~XXXXXXXXXX~~ AT 0.15%

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS (D + 7)										MEAN	T. ATROL.
3												34

3
0.05

POTENTIAL ORAL : 34

MEAN

34.9

10	20	30	40	50	60	70	80	90	100
T. suppression									

Principal Investigator : Professor W. Peters

Department of Medical Parasitology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

1961-62

COMPOUND : LUN 1720 WR 182234 BE 17580
FORMULATION : DISSOLVED & SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium jellii indonesiensis
VERTEBRATE HOST : ♂ FWH MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXX~~ ~~XXXXXXXXXX~~ ; NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2760 DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7											MEAN	% CONTROL
2	15	26	14	73	82	37	17	22	34	38	35.8	100	
0.05	45	16	41	21	50	16	32	14	66	22	32.3	90.2 ± 6.1	

~~XXXXXXXXXXXX~~ ~~XXXXXXXXXX~~ INACTIVE AT D+5 & 7

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7											MEAN	% CONTROL
2													100

2
0.05

SPOROZOICIDAL INDEX (%)

100

100

100% suppression

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

Table 6.1

COMPOUND : LCN 1721 WR 211814 ZP 12775
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigritensis
VERTEBRATE HOST : ♂ FFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2760 DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	CONTROL
1	15	26	14	73	82	37	17	22	34	38	35.3	10
0.05	10	42	20	18	13	30	23	39	45	19	25.9	72.3 ± 7.1

~~XXXXXXXXXXXX~~ - SLIGHTLY ACTIVE ~~XXXXXXXX~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	CONTROL
1												10

1
0.05

RESISTANCE INDEX

100%

50%

10	20	30	40	50	60	70	80	90	100
% suppression									

Principal Investigator : Professor W. Peters
Department of Medical Parasitology,
London School of Hygiene & Tropical Medicine

- 426 -

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1
0.05

APPENDIX A

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88

SUMMARY OF ANTIMALARIAL TESTS

TABLE 16.9

SPOROZOICIDAL ACTIVITY

UNFACED : LCN 1724 WR 228583 ZN 78910

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS

PARASITE : *Plasmodium yoelii* *yoelii*

VERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER : 2776

DATE : 6.6.84

PRELIMINARY TEST

CONCENTRATION(%)	DOCT COUNTS 0-7										MEAN	T. CONTROL
0	6	16	25	20	15	24	13	12	22	17	20.7	0
	58											
0.05	7	18	17	15	11	8	19	9	7	11	12.5	48.3 ± 5.1

~~XXXXXXXXXX~~ ACTIVE ~~XXXXXXXXXXXXXXXXXXXX~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	DOCT COUNTS 0-7										MEAN	T. CONTROL
0												0

0
0.05

0 10 20 30 40 50 60 70 80 90 100
% suppression

SPOROZOICIDAL ACTIVITY

0.05%

0.05%

Principal Investigator : Professor W. Peters

Department of Medical Microbiology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

TABLE 7.0

COMPOUND : LDN 1725 WR 233627 BH 13989
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : 3 FEM MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXXXXXXXX~~ : NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2776 DATE : 6.6.84

PRELIMINARY TEST

CONCENTRATION (M)	OOCYST COUNTS D + 7										MEAN	CONTROL
2	6	16	25	20	15	24	13	12	22	17	20.7	100
	58											
0.05	4	9	6	12	16	2	15	12	1		8.6	41.6 ± 6.1

~~VERY ACTIVE / ACTIVE / XKBKXKXKXKXKXKXKXKX~~ AT 0.05 M

EXTENDED TEST

CONCENTRATION (M)	OOCYST COUNTS D + 7										MEAN	CONTROL
2												100

2	
0.05	
	1 2 3 4 5 6 7 8 9 10
	3 suppression

Pre-treatment (day 0)

day

day

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

COMPOUND : LIN 1726 WR 235485 BH 35770
 FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
 ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
 PARASITE : Plasmodium yoelii nigeriensis
 VERTEBRATE HOST : 3 FFW MICE INVERTEBRATE HOST : Anopheles stephensi
 TOXICITY : ~~TOXIC TO MOSQUITOES~~ NO TOXIC EFFECTS SEEN
 EXPERIMENT NUMBER : 2776 DATE : 6.6.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	CONTROL
2	6	16	25	20	15	24	13	12	22	17	20.7	20
	58											
0.05	5	13	3	3	9	17	15	19	11	7	10.7	51.7 ± 7.7

~~XXXXXXXXXX~~ ACTIVE / ~~XXXXXXXXXX~~ AT DISEASE

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	CONTROL
2												20

2	
0.05	
Suppression	

SPOROZOICIDAL INDEX : 100

REC₅₀

REC₉₀

Principal Investigator : Professor W. Petens
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPRONTOXICAL ACTIVITY

COMPOUND: LA 1727 WR 232605 SH 69990
 FORMULATION: DISCOURD / SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
 ROUTE: ORAL ADMINISTRATION TO MOUTHPIECES IN SUCROSE FEED FOR 7 DAYS
 PARASITE: Plasmodium yoelii subparvius
 VERTEBRATE HOST: ♂ FWA MICE INVERTEBRATE HOST: Aedes albopictus
 TOXICITY: ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
 EXPERIMENT NUMBER: 2776 DATE: 6.6.84

PRELIMINARY TEST

CONCENTRATION %	DOXMT COUNTS 0 + 7										MEAN	STDEV.
2	8	16	25	20	15	24	13	12	22	17	20.7	4
	58											
0.05	33	7	21	10	11	16	6	15	6	4	16.8	23.7 ± 3.7
	19	16										

~~XXXXXXXXXXXXXXXXXXXX~~ INACTIVE AT 0.05 %

EXTENDED TEST

CONCENTRATION %	DOXMT COUNTS 0 + 7										MEAN	STDEV.
2												4

2												
0.05												
S. praecox												

AS MOUTHPIECES

100%

100%

Principal Investigator: Professor W. Peters
 Department of Medical Microbiology
 School of Medicine & Tropical Medicine

— 1992

[illegible][illegible][illegible][illegible]

1
0.05

Figure 1. Schematic representation of the experimental design. The subjects were divided into two groups: the control group and the experimental group. The control group was divided into two subgroups: the control group and the experimental group. The experimental group was divided into two subgroups: the control group and the experimental group. The control group was divided into two subgroups: the control group and the experimental group. The experimental group was divided into two subgroups: the control group and the experimental group.

10

93

PRIMARY ANTIVIRAL TESTS

FILE # 10

(SPOROZOICAL ACTIVITY)

UNWASHED - 10000 WR 247705 BU 51779

HUMILIATION - SUSPENDED - SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION

NOTE: ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE - Plasmodium falciparum

INVERTEBRATE HOST - ♀ TEA MOSE

INVERTEBRATE HOST - Anopheles stephensi

TOXICITY - ~~XXXXXX~~ ~~XXXXXX~~ ~~XXXXXX~~ NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER 2776

DATE: 6.6.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	ST. DEV.
2	6	16	25	20	15	24	13	12	22	17	20.7	
	58											
0.05	7	2	8	10	7	11	7	2	11	3	6.8	20.8 ± 8.1

XXXXXX ACTIVE / XXXXXXXX ACTIVE / XXXXXXXX AT DISEASE

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	ST. DEV.
2												

2
0.05

ANALYSIS OF VARIANCE

ANALYSIS OF TEST RESULTS

ANALYSIS OF TEST RESULTS

AD-A185 118

CHEMOTHERAPY OF RODENT MALARIA(U) LONDON SCHOOL OF
HYGIENE AND TROPICAL MEDICINE (ENGLAND) DEPT OF MEDICAL
PROTOZOOLOGY W PETERS JUL 85 DAMD17-84-C-4018

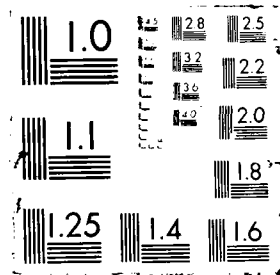
2/3

UNCLASSIFIED

F/G 6/15

NL





76

PRELIMINARY TEST

[illegible]

*FBLX X *ARTX *X X *ARTX *X X *SK IGNTX *ARTX *X X INACTIVE AT 0.25 7

EXTENDED TEST

[illegible]

x	y suppression
0	0.05

96

• 22 77

INVERTEBRATE HOST *Anopheles stephensi*.

DATE 13.6.84

			Y
20	24	21	
8	16	21	

[illegible]

[illegible]

Figure 1

			4
20	21		
12	20		

[illegible]

SUMMARY OF ANTIMALARIAL TESTS

4-17-64

SPOROZOIDAL ACTIVITY

PHONE NO. 1734 WR 242511 AA BH 89438

FORMULATION DISCLOSED SUSPENDED IN 1% AQUEOUS DEXTRE SOLUTION

ROUTE ORAL ADMINISTRATION TO MOSQUITOES IN COURSE FEEDING PLAYS

PARASITE Plasmodium vivax (Gibson)

VERTEBRATE HOST PEROMYSCUS

INVERTEBRATE HOST ANOPHELES

STATUS XX

EXPERIMENT NUMBER 2796

DATE 10-16-64

PRELIMINARY TEST

CONCENTRATION	DAYS POST-EXPOSURE												1	2
1	11	16	22	27	34	40	47	54	61	68	75	82		
	31	36												
2	13	17	24	31	38	45	52	59	66	73	80	87		
	15	19												

FULLY ACTIVE X ACTIVE X MODERATELY ACTIVE X INACTIVE

DEFINITIVE TEST

CONCENTRATION	DAYS POST-EXPOSURE												1	2
1														

1. Name of Investigator: _____
 2. Name of Institution: _____
 3. Address: _____

5. 911

22-47188 1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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11. 11. 1991

SUMMARY OF ANTIMALARIAL TESTS
SPORONTICIDAL ACTIVITY

TABLE 51

COMPOUND: WLN 1751 WR 194343 ZN 41968
 FORMULATION: DISSOLVED & SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
 ROUTE: ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS
 PARASITE: Plasmodium falciparum
 VERTEBRATE HOST: 3 WEEK MICE INVERTEBRATE HOST: Aedes triseriatus
 TOXICITY: TOXIC TO A. triseriatus, 40.0% ~~TOXIC TO A. triseriatus~~ 50% mortality
 EXPERIMENT NUMBER: 2796 DATE: 13.6.84

PRELIMINARY TEST

CONCENTRATION %	DOSE CONTROL 0 + 1											MEAN	ST. DEV.
2	41	16	12	40	14	12	19	42	20	24	20.3		
	31	15											
0.6	37	13	18	12	15	18					17.0	70.1	1.0

~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~

INTERPRETATION

CONCENTRATION %	DOSE CONTROL 0 + 1											MEAN	ST. DEV.
2													

2	
0.05	
EXPERIMENTAL DATA	

EXPERIMENTAL DATA

100

100

92

92

92

92

92

92

92

92

92

92

92

92

92

92

92

9292

92

92

92

SUMMARY OF ANTIMALARIAL TESTS
SPOROZONICIDAL ACTIVITY

TABLE 8.3

COMPOUND : LON 1940 WR 199508 ZP 43350
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ FFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2830 DATE : 27.6.84

PRELIMINARY TEST

CONCENTRATION(%)	DOOYST COUNTS 0 + 7											MEAN	% CONTROL
2	30	19	32	25	41	21	10	13	9	28	24.9	100	
	46												
0.05	4	14	12	6	4	3	60	33	19	33	17.3	69.3 ± 8.8	
	16	3											

~~XXXXXXXXXXXX~~ SLIGHTLY ACTIVE ~~XXXXXXXXXX~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	DOOYST COUNTS 0 + 7											MEAN	% CONTROL
2													100

2
0.05

SPOROZONICIDAL ACTIVITY

40%

40%

Principal Investigator : Professor A. Peters
Department of Medical Entomology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROANTOCIDAL ACTIVITY

- TABLE 8.1

COMPOUND : LOH 1931 WR 249725 BK 69990
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ TFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2830 DATE : 27.6.84

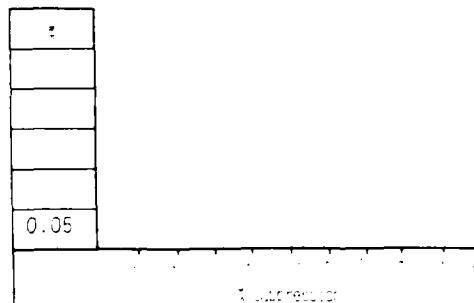
PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
2	30	19	32	25	41	21	10	13	9	28	24.9	100
	46											
0.05	12	14	8	13	1	14	10	16	7	11	10.6	42.6 ± 6.0

~~XXXXXXXXXXXX~~ ACTIVE / ~~XXXXXXXXXXXX~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
2												100



SPOROANTOCIDAL DOSE : 100

LD50 :

LD90 :

Principal Investigator : Professor A. K. Sengupta
Department of Medical Microbiology
Indian School of Advanced Studies in Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOIDAL ACTIVITY

TABLE 85

COMPOUND : JCN 1932 WR 251855 AA BK 71178
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ TFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : TOXIC TO A. stephensi AT .05% : ~~XXXXXXXXXXXX~~ 92 % mortality
EXPERIMENT NUMBER : 2830 DATE : 27.6.84

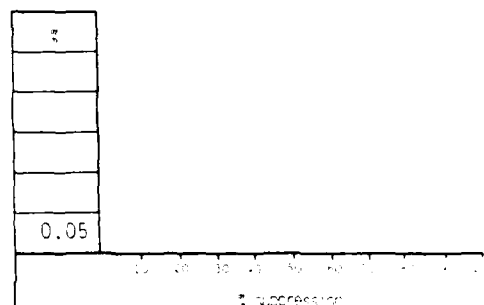
PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
J	30	19	32	25	41	21	10	13	9	28	24.9	100
	46											
0.05	18	12									15.0	60.2

~~XXXXXXXXXXXX~~ / ACTIVE / ~~XXXXXXXXXXXX~~ ~~XXXXXXXXXXXX~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
J												100



(SPOROZOIDAL DOSE - JCN)

(0.05%)

(0.05%)

Principal Investigator : Professor A. Peters
Department of Medical Entomology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 86

SPOROANTICIDAL ACTIVITY

COMPOUND : LON 1884 Ph 4007 BK 64306
 FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
 ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
 PARASITE : Plasmodium yoelii nigeriensis
 VERTEBRATE HOST : ♂ TFW MICE INVERTEBRATE HOST : Anopheles stephensi
 TOXICITY : TOXIC TO A. stephensi AT .05% ; ~~NO TOXIC EFFECTS SEEN~~ 100 % mortality
 EXPERIMENT NUMBER : 2816 DATE : 20.6.84

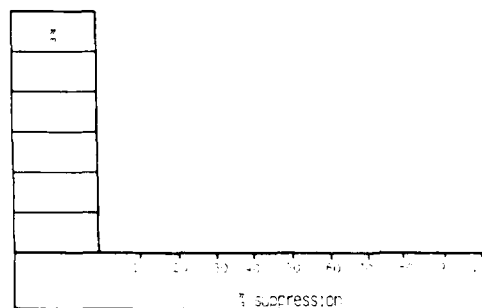
PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
0	15	56	19	16	16	15	14	18	19	26	21.4	100
0.05												TOXIC

FULLY ACTIVE / ACTIVE / SLIGHTLY ACTIVE / INACTIVE AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
0												100



SPOROANTICIDAL DOSE (SD)

SD₅₀ :

SD₉₀ :

Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZONICIDAL ACTIVITY

TABLE 87

COMPOUND : LON 1885 Ph 4017 BK 64315
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ FFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : TOXIC TO A. stephensi AT 0.05 % ; ~~NO TOXIC EFFECTS SEEN~~ 80 % mortality
EXPERIMENT NUMBER : 2816 DATE : 20.6.84

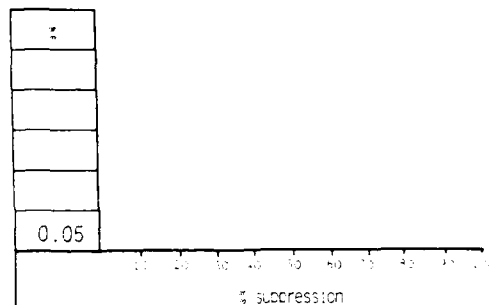
PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
3	15	56	19	16	16	15	14	18	19	26	21.4	100
0.05	45	79	6	3	64	31					38.0	100 ± 13.1

~~ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK~~ INACTIVE AT 0.05 %

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
3												100



SPOROZONICIDAL DOSE : 100

LD50 :

LD90 :

Principal Investigator : Professor W. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

W: S S

COMPOUND : LON 1886 Ph 4900 BK 64324

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : Plasmodium yoelii nigeriensis

VERTEBRATE HOST : ♂ THW MICE

INVERTEBRATE HOST : Anopheles stephensi

TOXICITY : TOXIC TO A. stephensi AT .05% : ~~NO TOXIC EFFECTS~~ 72 % mortality

EXPERIMENT NUMBER : 2816

DATE : 20.6.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
0	15	56	19	16	16	15	14	18	19	26	21.4	100
0.05	12	17	18	14	12	10	8				13.0	60.7 ± 4.7

~~NO TOXIC EFFECTS~~ ACTIVE / ~~NO TOXIC EFFECTS~~ / INACTIVE AT 0.05 %

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
0												100

0
0.05

SPOROZOICIDAL INDEX (S.I.)

50000

50000

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

- 89

SPOROICIDAL ACTIVITY

COMPOUND : LON 1887 Ph 4901 BK 64333

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : *Plasmodium yoelii nigeriensis*

VERTEBRATE HOST : 3 FWH MICE

INVERTEBRATE HOST : *Anopheles stephensi*TOXICITY : TOXIC TO *A. stephensi* AT 0.05% ; ~~XXXXXXXXXXXX~~ 92 % mortality

EXPERIMENT NUMBER : 2816

DATE : 20.6.84

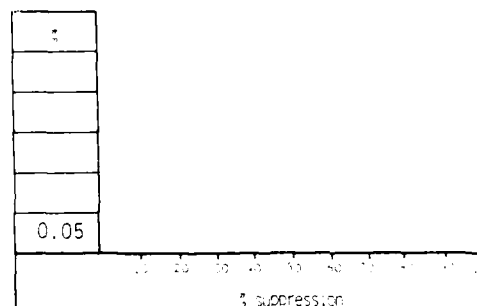
PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS 3 + 7										MEAN	% SUPPRESSION
2	15	56	19	16	16	15	14	18	19	26	21.4	0
0.05	100	58									79.0	100

~~XXXXXXXXXXXX~~ INACTIVE AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS 3 + 7										MEAN	% SUPPRESSION
2												0



SPOROICIDAL INDEX

2000

2000

Principal Investigator : Professor W. Peters

Department of Medical Protozoology

London School of Hygiene & Tropical Medicine

90

		٧٤
٢٤	٢٥	
٢٦	٢٧	

[illegible]

• 1 •

1. THE UNITED STATES OF AMERICA
 2. DO HEREBY DECLARE THAT THE UNITED STATES OF AMERICA
 3. DO NOT RECOGNIZE THE GOVERNMENT OF THE PEOPLES REPUBLIC OF CHINA
 4. AS THE LEGITIMATE GOVERNMENT OF CHINA
 5. AND DO RECOGNIZE THE GOVERNMENT OF THE REPUBLIC OF CHINA
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 59. AND DO RECOGNIZE THE GOVERNMENT OF

[illegible]

1. *Chlorophyll a* (Chl *a*)

[illegible]

1 1 1

1. *Pharmaceutical industry* – The pharmaceutical industry is the largest of the three industries, with sales of \$10.5 billion in 1997. It is the only industry that has not experienced a decline in sales since 1990. The industry is dominated by a few large firms, with the top five firms accounting for 40% of sales. The industry is highly competitive, with many firms competing for market share.

• 204 • (1) 人、鬼、魔、妖、怪 人

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Figure 1 shows a schematic diagram of a multi-layered structure. It consists of five horizontal layers, labeled A, B, C, D, and E from top to bottom. Each layer contains a series of dots arranged in a regular grid pattern. The layers are separated by horizontal lines. The dots are arranged in a regular grid pattern across the layers.

[illegible]

$$f = f_1 + f_2 + \dots$$

Journal of Management Education 30(6)

YAK-X-ALBANY-X-2

DATE OF BIRTH: 1940-01-01

[illegible]

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1. *Journal of Management Education*, 2000, 24(1), 1-10.
 2. *Journal of Management Education*, 2000, 24(1), 11-20.
 3. *Journal of Management Education*, 2000, 24(1), 21-30.

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1. *Chlorophyll a* (Chl *a*)

A blank sheet of graph paper with a grid pattern. The grid consists of small squares formed by thin black lines. There are approximately 20 columns and 15 rows of squares visible on the page. The paper is otherwise empty of any markings or text.

SUMMARY OF ANTIMALARIAL TESTS
PORTAL CIRCULAR ACTIVITY

SUMMARY: LAM 1741 WR 102796 AD BC 78878

FORMULATION: DISSOLVED - SUSPENDED IN 5% AQUEOUS SUSPENSION

ROUTE: ORAL ADMINISTRATION TO MOSQUITOES ON SOURCE FEED FOR 7 DAYS

PARASITE: Plasmodium falciparum

INTESTINATE HOST: CEP-100

INTESTINATE HOST: Supernova

TESTING: 100% to 100% at 10% AM 4000X 0000000000 40 mortality

EXPERIMENT NUMBER: 2796 DATE: 13.6.84

CELLULARITY TEST

CONCENTRATION %	100% ATD 100%										MEAN	ADJ.
1	41	16	12	40	14	12	12	42	20	24	22.5	1
2	31	16										
3	17	22	29	11	7	6					20.5	65.0
4												

0000 0000 0000 0000 0000 0000 0000 0000 0000 0000

CELLULARITY TEST

CONCENTRATION %	100% ATD 100%										MEAN	ADJ.
1												1
2												
3												
4												
5												
6												
7												
8												
9												
10												

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1. The test was performed in a 100% ATD 100%
2. The test was performed in a 100% ATD 100%
3. The test was performed in a 100% ATD 100%

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOIDIAL ACTIVITY

WELL 9.9

COMPOUND: LON 1716 WR 9792 AU 63248
FORMULATION: DISSOLVED / SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
ROUTE: ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE: *Plasmodium yoelii* *oberlensis*
VERTEBRATE HOST: 2 FEMALE
INVERTEBRATE HOST: *Anopheles stephensi*
TOXICITY: ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER: 2760 DATE: 30.5.84

PRELIMINARY TEST

CONCENTRATION %	DOCT COUNT 0 + 7										MEAN	CONTROL
2	15	26	14	73	82	37	17	22	34	38	35.8	4.1
0.5	30	27	40	13	36	18	35	22	64	16	30.7	35.8 ± 5.0

~~XXXXXXXXXXXXXXXXXXXX~~ INACTIVE AT DOSE 2

EXTENDED TEST

CONCENTRATION %	DOCT COUNT 0 + 7										MEAN	CONTROL
2												4.1

1
DOSE

SPOROZOIDIAL ACTIVITY

40%

10%

XXXXXXXXXXXXXXXXXXXX
To suppress

Includes Investigation of toxicity with other
Department of Veterinary Microbiology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

100

COMPOUND : LON 1718 WR 158124 BD 22997
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ TFW MICE (INVERTEBRATE HOST : Anopheles stephensi)
TOXICITY : ~~TOXIC TO EXPERIMENTAL MICE~~; NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2760 DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
0	15	26	14	73	82	37	17	22	34	38	35.8	100
0.05	18	16	17	26	20	33	24	16			21.3	59.4 ± 4.7

~~POORLY~~ ACTIVE / ~~INACTIVE~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	% CONTROL
0												100

0
0.05

SPOROZOICIDAL ACTIVITY

20%

20%

0	0.05	0.1	0.2	0.5	1	2	5	10	20	50	100
% suppression											

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

TABLE 101

COMPOUND : LON 1909 WR 203659 ZN 39913
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ TFH MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXX~~ ~~XXXXXXXXXX~~ ; NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2830 DATE : 27.6.84

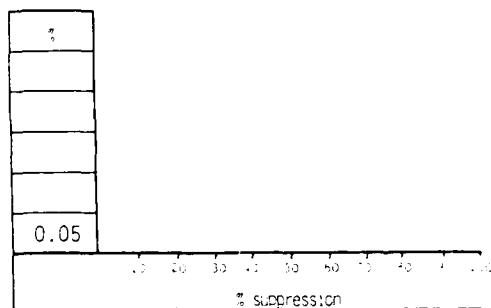
PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7											MEAN	% CONTROL
2	30	19	32	25	41	21	10	13	9	28	24.9	100	
	46												
0.05	47	10	60	101	72	37	23	22	6	13	37.4	100 ± 7.6	

~~XXXXXXXXXX~~ ~~XXXXXXXXXX~~ ~~XXXXXXXXXX~~ / INACTIVE AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7											MEAN	% CONTROL
2													100



SPOROZOICIDAL ACTIVITY

100%

100%

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

5.5 DRUG INTERACTION TEST DATA

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 102

COMPOUND NAME Mefloquine (M) +
OR NUMBER Spiramycin (SP)..... PARASITE (SUB)SPECIES P. berghei....
FORMULATION Tween 80 / H₂O. ROUTE OF ADMINISTRATION : SC/TP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	M 0.5 + SP 3.0	5		-	80.0 ± 11.7
	M 1.0 + SP 3.0	5		-	75.7 ± 9.7
N	M 2.0 + SP 3.0	5	1	-	46.2 ± 7.9
	M 3.0 + SP 3.0	5		-	2.7 ± 0.9
	Ø	10		14.9	
ED ₅₀ (range) 1.1 (0.6 - 2.1)					
ED ₉₀ (range) 2.7 (1.7 - 5.3)					
Resistance factor I ₉₀					
	M 0.5 + SP 10.0	5		-	22.7 ± 4.3
	M 1.0 + SP 10.0	5		-	20.1 ± 7.0
N	M 3.0 + SP 10.0	5	1	-	16.4 ± 1.0
	M 10.0 + SP 10.0	5		-	2.7 ± 0.6
	Ø	10		14.9	
ED ₅₀ (range) 0.4 (0.2 - 0.7)					
ED ₉₀ (range) 1.4 (0.7 - 2.7)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 100

COMPOUND NAME Mefloquine (M) +
OR NUMBER ..Spiramycin (SP)..... PARASITE (SUB)SPECIES ...P. berghei.....
FORMULATION Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	M 0.5 + SP 30.0	5		-	4.0 ± 0.7
	M 1.0 + SP 30.0	5		-	4.0 ± 1.9
N	M 2.0 + SP 30.0	5	1	-	2.7 ± 0.9
	M 3.0 + SP 30.0	5		-	2.0 ± 1.0
	Ø	10		14.9	
ED ₅₀ (range) < 0.5					
ED ₉₀ (range) < 0.5					
Resistance factor I ₉₀					
	M 0.5 + SP 60	5		-	0.6 ± 0.3
	M 1.0 + SP 60	5		-	1.3 ± 0.7
N	M 2.0 + SP 60	5	1	-	1.0 ± 0.2
	M 3.0 + SP 60	5		-	1.3 ± 0.7
	Ø	10		14.9	
ED ₅₀ (range) < 0.5					
ED ₉₀ (range) < 0.5					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL RESULTS
 SECOND SUBMITTAL

10

COMPOUND NAME Spiramycin (SP) +
 DR NUMBER Mefloquine PARASITE P. berghei
 FORMULATION Tween 80 / H₂O ROUTE OF ADMINISTRATION sc + ~~oral~~
 MAXIMUM TOLERATED DOSE MTD MG/KG

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Tested test control %
	SP 3.0 + M 0.5	5		-	80.0 ± 11.7
	SP 10.0 + M 0.5	5		-	22.7 ± 4.3
N	SP 30.0 + M 0.5	5	1	-	4.0 ± 0.7
	SP 60.0 + M 0.5	5		-	0.6 ± 0.3
	Ø	10		14.9	
ED ₅₀ (range) 5.3 (4.0 - 12.0)					
ED ₉₀ (range) 19.8 (12.5 - 36.5)					
Resistance factor I ₉₀					
	SP 3.0 + M 1.0	5		-	75.7 ± 9.7
	SP 10.0 + M 1.0	5		-	20.1 ± 7.0
N	SP 30.0 + M 1.0	5	1	-	4.0 ± 1.2
	SP 60.0 + M 1.0	5		-	1.3 ± 0.7
	Ø	10		14.9	
ED ₅₀ (range) 5.0 (2.5 - 10.5)					
ED ₉₀ (range) 22.5 (11.5 - 47)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
BLOOD PHOSPHATIDASE

TABLE 105

COMPOUND NAME Spiramycin (SP) +
Mefloquine (M) PARASITE SUB SPECIES P. berghei
 FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION SC
 MAXIMUM TOLERATED DOSE (MTD) MG/KG

Strain	Daily dose mg/kg 00-0+0	No. of mice	No. of experiments	Mean control parasite rate %	Tested Controls
	SP 3.0 + M 2.0	5		-	46.2 ± 7.9
	SP 10.0 + M 2.0	5		-	16.4 ± 1.0
N	SP 30.0 + M 2.0	5	1	-	2.7 ± 0.9
	SP 60.0 + M 2.0	5		-	1.0 ± 0.2
	Ø	10		14.9	

ED₅₀ range 2.4 (1.4-3.5)

ED₉₀ range 15.0 (9.0-22.5)

Resistance factor 1.1

	SP 3.0 + M 3.0	5		-	2.7 ± 0.9
	SP 10.0 + M 3.0	5		-	2.7 ± 0.6
N	SP 30.0 + M 3.0	5	1	-	2.0 ± 1.0
	SP 60.0 + M 3.0	5		-	1.3 ± 0.7
	Ø	10		14.9	

ED₅₀ range < 3.0

ED₉₀ range < 3.0

Resistance factor 1.1

Principal Investigator: Professor W. Miller
 Department of Medical Microbiology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD CONCENTRATIONS)

TABLE 106

COMPOUND NAME

DR NUMBER Halofantrine PARASITE (SUB) SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION sc

MAXIMUM TOLERATED DOSE (MTD) MG/KG (X)

Strain	Daily dose mg/kg SC-SC	No. of mice	No. of experiments	Mean control parasite rate %	Treated control
	0.03	5		-	90.6 ± 3.1
	0.1	5		-	70.6 ± 2.9
N	0.3	5	1	-	61.0 ± 5.0
	1.0	5		-	9.2 ± 6.9
	3.0	5		-	0.6 ± 0.5
	Ø	10		23.1	

LD₅₀ 0.2 (0.1 - 0.5)

LD₅₀ 0.8 (0.3 - 1.6)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

Principal Investigator: Professor W. J. J. van der
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL RESULTS
 80001-80010 (1000)

1000

COMPOUND NAME

DR. NUMBER Spiramycin PARASITE P. berghe

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION per os

MAXIMUM TOLERATED DOSE (MTD) 1000 MG/KG (X)

Strain	Daily dose mg/kg 00-0+3	No. of mice	No. of experiments	Mean (S.D.) parasite rate %	Mean (S.D.) parasite rate %
	10	5		-	87.0 ± 4.9
	30	5		-	84.8 ± 7.1
N	100	5	1	-	52.9 ± 5.9
	300	5		-	83 ± 3.3
	1000	5		-	17 ± 0.6
	Ø	10		23.1	

ED₅₀ (range) 6.2 (2.7-18.8)

ED₃₀ (range) 26.0 (11.3-78.0)

Resistance factor 130

ED₅₀ (range)

ED₃₀ (range)

Resistance factor 130

Principal Investigator: Professor W. H. Waters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

Spiramycin (SP) +
 Halofantrine (H)
 Tween 80 / H₂O

				Mean	SD
N	SP 10 + H 0.03	5	-	94.5 ± 3.4	
	SP 30 + H 0.03	5	-	82.5 ± 4.9	
	SP 100 + H 0.03	5	-	45.8 ± 4.9	
	SP 300 + H 0.03	5	-	4.9 ± 2.2	
	SP 1000 + H 0.03	5	-	3.4 ± 0.7	
	Ø	10	23		

60 (25-128)

300 (130-640)

N	SP 10 + H 0.1	5	-	90.0 ± 6.0	
	SP 30 + H 0.1	5	-	70.1 ± 7.7	
	SP 100 + H 0.1	5	-	37.5 ± 7.9	
	SP 300 + H 0.1	5	-	9.1 ± 3.7	
	SP 1000 + H 0.1	5	-	2.2 ± 0.9	
	Ø	10	23		

ED₅₀ range 58 (3.4 - 90)

ED₉₀ range 29.0 (17.0 - 45.0)

Resistance factor I₉₀

Principal Investigator: Professor W. J. J. J.
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

P. Dengue

[illegible]

1990

Figure 1 is a schematic representation of the experimental design. It shows a sequence of three events: 1. A subject is presented with a stimulus (a face). 2. A response is recorded (a button press). 3. A reward is delivered (a coin). The sequence is labeled 1, 2, and 3 respectively.

23

255(100-470)

SP10 + H10 . 5 52 + 35

22

range 0.8(0.4 - 1.8)

100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 2100 2200 2300 2400 2500 2600 2700 2800 2900 3000 3100 3200 3300 3400 3500 3600 3700 3800 3900 4000 4100 4200 4300 4400 4500 4600 4700 4800 4900 5000 5100 5200 5300 5400 5500 5600 5700 5800 5900 6000 6100 6200 6300 6400 6500 6600 6700 6800 6900 7000 7100 7200 7300 7400 7500 7600 7700 7800 7900 8000 8100 8200 8300 8400 8500 8600 8700 8800 8900 9000 9100 9200 9300 9400 9500 9600 9700 9800 9900 10000

Principal Investigator: Professor Whitten,
Department of Medical Protozoology,
London School of Hygiene & Tropical Medicine

Halofantrine (HA) + Spiramycin (SP) P. berghei

Halofantrine (HA) + Spiramycin (SP)

P. berghei

Tween 80/H₂O

Halofantrine (HA) + Spiramycin (SP)

Halofantrine (HA) + Spiramycin (SP)

HA	SP	N	Mean	SD	Mean	SD
H003	SP10	5	945	± 34		
H01	SP10	5	900	± 60		
N	H03	SP10	5	848	± 13	
	H0	SP10	5	52	± 35	
	H30	SP10	5	0		
	Ø	10	231			

02(0.07-0.6)

06(0.2-1.5)

Halofantrine (HA) + Spiramycin (SP)

H003	SP30	5	825	± 49		
H01	SP30	5	701	± 77		
N	H03	SP30	5	650	± 81	
	H10	SP30	5	22	± 17	
	H30	SP30	5	0		
	Ø	10				

01(0.05-0.5)

04(0.1-1.3)

Halofantrine (HA) + Spiramycin (SP)

Principal Investigator: Professor A. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
BLOOD CONCENTRATIONS

TABLE 111

COMPOUND NAME Halofantrine (H) +
DR NUMBER Spiramycin (SP) PARASITE SUBSPECIES *P. berghei*
FORMULATION Tween 80 / H₂O ROUTE OF ADMINISTRATION : SC ~~IP-0077~~
MAXIMUM TOLERATED DOSE MTD MG/KG X ...

Strain	Daily dose mg/kg DC-0+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated $\frac{PM}{100}$ control $\frac{PM}{100}$
	H 0.03 + SP 10.0	5		-	45.8 ± 4.9
	H 0.1 + SP 10.0	5		-	37.5 ± 7.9
N	H 0.3 + SP 10.0	5	1	-	46.1 ± 3.9
	H 1.0 + SP 10.0	5		-	0
	H 3.0 + SP 10.0	5		-	0
	Ø	10		23.1	

ED₅₀ (range) 0.07 (0.03-0.3)

ED₉₀ (range) 0.2 (0.06-0.6)

Resistance factor i₉₀

	H 0.03 + SP 30.0	5		-	4.9 ± 2.2
	H 0.1 + SP 30.0	5		-	9.1 ± 3.7
N	H 0.3 + SP 30.0	5	1	-	8.7 ± 3.2
	H 1.0 + SP 30.0	5		-	0
	H 3.0 + SP 30.0	5		-	0
	Ø	10		23.1	

ED₅₀ (range) 0.015 (0.004-0.03)

ED₉₀ (range) 0.09 (0.02-0.1)

Resistance factor i₉₀

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 112

COMPOUND NAME

OR NUMBER ..HALOFANTRINE..... PARASITE (SUB)SPECIES ...P. berghei...

FORMULATION Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >1.0.. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% X100
	0.1	5		-	91.7 ± 2.9
	0.3	5		-	75.3 ± 6.3
N	0.5	5	1	-	66.0 ± 9.4
	1.0	5		-	26.2 ± 7.6
	Ø	10		23.6	
ED ₅₀ (range) 0.5 (0.3 - 1.2)					
ED ₉₀ (range) 1.2 (1.0 - 3.5)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 113

COMPOUND NAME

OR NUMBER ..SPIRAMYCIN..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >20... MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% 100
	5.0	5		—	83.3 ± 1.8
	10.0	5		—	61.2 ± 8.4
N	15.0	5	1	—	45.3 ± 11.4
	20.0	5		—	39.4 ± 3.9
	Ø	10		23.6	
ED ₅₀ (range) 13.5 (9.0 - 18.0)					
ED ₉₀ (range) 15.0 (13.0 - 17.0)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 111

COMPOUND NAME HALOFANTRINE +

OR NUMBER SP1RAMYCIN..... PARASITE (SUB)SPECIES *P. berghei*....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 5.0	5		-	68.6 ± 9.7
	0.3 + 5.0	5		-	41.5 ± 2.8
N	0.5 + 5.0	5	1	-	40.6 ± 3.0
	1.0 + 5.0	5		-	13.0 ± 7.9
	Ø	10		23.6	
ED ₅₀ (range) 0.27 (0.12 - 0.5)		0.64 / 0.17			
ED ₉₀ (range) 1.1 (0.5 - 2.1)					
Resistance factor I ₉₀					
	0.1 + 10.0	5		-	47.2 ± 5.6
	0.3 + 10.0	5		-	47.9 ± 5.6
N	0.5 + 10.0	5	1	-	42.2 ± 3.6
	1.0 + 10.0	5		-	1.9 ± 0.2
	Ø	10		23.6	
ED ₅₀ (range) 0.35 (0.26 - 0.48)		0.38 / 0.12			
ED ₉₀ (range) 0.65 (0.5 - 0.92)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 115

COMPOUND NAME HALOFANTRINE +

OR NUMBER SP. RAMMISIN..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% $\times 100$
	0.1 + 15.0	5		-	84.1 \pm 2.4
	0.3 + 15.0	5		-	67.4 \pm 9.5
N	0.5 + 15.0	5	1	-	42.0 \pm 11.0
	1.0 + 15.0	5		-	11.0 \pm 3.7
	\emptyset	10		23.6	
ED ₅₀ (range) 0.3(0.18 - 0.52)		0.47 / 0.25			
ED ₉₀ (range) 0.8(0.5 - 1.4)					
Resistance factor I ₉₀					
	0.1 + 20.0	5		-	73.7 \pm 8.8
	0.3 + 20.0	5		-	38.1 \pm 4.6
N	0.5 + 20.0	5	1	-	34.8 \pm 4.5
	1.0 + 20.0	5		-	2.1 \pm 1.0
	\emptyset	10		23.6	
ED ₅₀ (range) 0.22(0.13 - 0.4)		0.32 / 0.5			
ED ₉₀ (range) 0.54(0.32 - 1.0)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 116

COMPOUND NAME SPIRAMYCIN +
OR NUMBER .HALOFANTHRINE..... PARASITE (SUB)SPECIES .P. berghei.....
FORMULATION ...Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	5.0 + 0.1	5		-	68.6 ± 9.7
	10.0 + 0.1	5		-	47.2 ± 5.6
N	15.0 + 0.1	5	1	-	84.1 ± 2.4
	20.0 + 0.1	5		-	73.7 ± 8.5
	Ø	10		23.6	
ED ₅₀ (range)		> 0.33 0.16			
ED ₉₀ (range) > 20					
Resistance factor I ₉₀					
	5.0 + 0.3	5		-	41.5 ± 2.8
	10.0 + 0.3	5		-	47.9 ± 5.6
N	15.0 + 0.3	5	1	-	67.4 ± 9.5
	20.0 + 0.3	5		-	38.1 ± 4.6
	Ø	10		23.6	
ED ₅₀ (range)		> 0.33 0.16			
ED ₉₀ (range) > 20					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 117

COMPOUND NAME SPIRAMYCIN +
OR NUMBER HALOFANTHINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	5.0 + 0.5	5		-	40.6 ± 3.0
	10.0 + 0.5	5		-	42.2 ± 3.6
N	15.0 + 0.5	5	1	-	42.0 ± 11.0
	20.0 + 0.5	5		-	34.8 ± 4.5
	Ø	10		23.6	
ED ₅₀ (range)		> 0.73 0.01			
ED ₉₀ (range) > 20					
Resistance factor I ₉₀					
	5.0 + 1.0	5		-	13.0 ± 7.9
	10.0 + 1.0	5		-	1.9 ± 0.2
N	15.0 + 1.0	5	1	-	11.0 ± 3.7
	20.0 + 1.0	5		-	2.1 ± 1.0
	Ø	10		23.6	
ED ₅₀ (range) ~ 1.0		0.10 10.0			
ED ₉₀ (range) ~ 6.2					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 11 -

COMPOUND NAME

OR NUMBER Halofantrine PARASITE SUB SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION PO

MAXIMUM TOLERATED DOSE (MTD) MG/KG X

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Mean test parasite rate %
	0.1	5		-	94.8 ± 5.2
	0.3	5		-	91.4 ± 2.0
N	1.0	5	1	-	51.6 ± 4.1
	3.0	5		-	0.1 ± 0.1
	∅	10		20.9	

ED₅₀(range) 0.5(0.1 - 1.3)

ED₉₀(range) 1.3(0.4 - 3.5)

Resistance factor I₉₀

ED₅₀(range)

ED₉₀(range)

Resistance factor I₉₀

Principal Investigator: Professor W. Peters
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Compound Name

IP Number Chloroquine Parasite Sub Species P. berghei

Formulation Tween 80/H₂O Route of Administration PO ~~IP~~

Maximum Tolerated Dose (MTD) 100 mg/kg

Strain	Daily dose mg/kg DD-D+3	No. of mice	No. of experiments	Mean control parasite rate %	reated $\bar{x} \pm s$
	0.1	5		-	82.8 \pm 4.1
	0.3	5		-	80.1 \pm 5.7
N	1.0	5	1	-	52.1 \pm 7.6
	3.0	5		-	24.3 \pm 8.5
	\emptyset	10		20.9	

ED₅₀ range 0.8 (0.2 - 2.1)

ED₉₀ range 3.1 (0.9 - 8.5)

Resistance factor 1₉₀

ED₅₀ (range)

ED₉₀ (range)

Resistance factor 1₉₀

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DATA

100 1 10

BLOOD SCHIZONTICIDIC

COMPOUND NAME Halofantrine (H) +

OR NUMBER- Chloroquine (CQ) PARASITE SUB SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION: i.p.

MAXIMUM TOLERATED DOSE (MTD) MG/KG

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated MTD control MTD
	H 0.1 + CQ 0.1	5		-	100 ± 2.5
	H 0.3 + CQ 0.1	5		-	88.8 ± 1.3
N	H 1.0 + CQ 0.1	5	1	-	50.2 ± 16.1
	H 3.0 + CQ 0.1	5		-	0.05 ± 0.05
	Ø	10		20.9	

ED₅₀ (range) 0.7 (0.4-1.2)ED₉₀ (range) 1.3 (0.8-2.3)Resistance factor I₉₀

	H 0.1 + CQ 0.3	5		-	98.6 ± 2.8
	H 0.3 + CQ 0.3	5		-	86.6 ± 4.8
N	H 1.0 + CQ 0.3	5	1	-	44.8 ± 13.6
	H 3.0 + CQ 0.3	5		-	0.3 ± 0.2
	Ø	10		20.9	

ED₅₀ (range) 0.6 (0.3-1.2)ED₉₀ (range) 1.3 (0.5-2.6)Resistance factor I₉₀

Principal Investigator: Professor W. Peters
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Summary of Antimalarial Drug Tests
Blood Schizonticide

Table 121

Compound Name Halofantrine (H) +
 Drug Number Chloroquine (CQ) PARASITE SUB SPECIES P. berghei
 Formulation Tween 80/H₂O ROUTE OF ADMINISTRATION i.p. ~~per os~~
 Maximum Tolerated Dose (MTD) MG/KG x

Strain	Daily dose mg/kg 00-0+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated vs. Control, %
	H 0.1 + CQ 1.0	5		-	89.0 ± 4.1
	H 0.3 + CQ 1.0	5		-	75.3 ± 3.1
N	H 1.0 + CQ 1.0	5	1	-	49.3 ± 11.3
	H 3.0 + CQ 1.0	5		-	0
	Ø	10		20.9	

ED₅₀ range 0.6 (0.2 - 1.1)
 ED₉₀ range 1.1 (0.3 - 1.9)
 Resistance factor I₉₀

	H 0.1 + CQ 3.0	5		-	81.1 ± 2.7
	H 0.3 + CQ 3.0	5		-	74.0 ± 4.0
N	H 1.0 + CQ 3.0	5	1	-	26.5 ± 6.4
	H 3.0 + CQ 3.0	5		-	0
	Ø	10		20.9	

ED₅₀ (range) 0.3 (0.1 - 0.8)
 ED₉₀ (range) 0.6 (0.3 - 1.9)
 Resistance factor I₉₀

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 122

COMPOUND NAME Chloroquine (CQ) +
OR NUMBER Halofantaine (H) PARASITE (SUB)SPECIES P. berghei
FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/1P/P0/1P
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR % Control PR %
	CQ 0.1 + H 0.1				100 ± 2.5
	CQ 0.3 + H 0.1				98.6 ± 2.8
N	CQ 1.0 + H 0.1				89.0 ± 4.1
	CQ 3.0 + H 0.1				81.1 ± 2.7
	Ø				
ED ₅₀ (range) 8.5(6.6 - 11.0)					
ED ₉₀ (range) 37.0(30.0 - 48.0)					
Resistance factor I ₉₀					
	CQ 0.1 + H 0.3				88.8 ± 1.3
	CQ 0.3 + H 0.3				86.6 ± 4.8
N	CQ 1.0 + H 0.3				75.3 ± 3.1
	CQ 3.0 + H 0.3				74.0 ± 4.0
	Ø				
ED ₅₀ (range) 7.8(1.5 - 27.0)					
ED ₉₀ (range) > 100					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 123

COMPOUND NAME Chloroquine (CQ) +
OR NUMBER Halofantrine (H)..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated Control
	CQ 0.1 + H 1.0				50.2 ± 16.1
	CQ 0.3 + H 1.0				44.8 ± 13.6
N	CQ 1.0 + H 1.0				49.3 ± 11.3
	CQ 3.0 + H 1.0				26.5 ± 6.4
	Ø				
ED ₅₀ (range) 0.2(<0.1 - 0.6)					
ED ₉₀ (range) 23.3(3.3 - 80)					
Resistance factor I ₉₀					
	CQ 0.1 + H 3.0				0.05 ± 0.05
	CQ 0.3 + H 3.0				0.3 ± 0.2
N	CQ 1.0 + H 3.0				0
	CQ 3.0 + H 3.0				0
	Ø				
ED ₅₀ (range) < 0.1					
ED ₉₀ (range) < 0.1					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

NAME: Primaquine PARASITE SUB SPECIES: P. berghei
 FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: SC
 MAXIMUM TOLERATED DOSE (MTD): 10 mg/kg

Strain	Dose mg/kg BW/day	No. of mice	No. of experiments	Mean control parasite rate %	Mean test parasite rate %
	0.1	5		-	92.5 ± 3.6
	0.3	5		-	93.1 ± 2.4
N	1.0	5	1	-	63.0 ± 5.1
	3.0	5		-	34.4 ± 4.0
	∅	10		20.8	

ED₅₀ range: 1.5 (1.1 - 2.2)
 ED₅₀ range: 5.8 (4.1 - 8.4)
 Resistance factor: 1

ED₅₀ range
 ED₅₀ range
 Resistance factor: 1

Principal Investigator: Professor W. Peters
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 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 125

COMPOUND NAME Halofantrine (H) +
DR NUMBER Primaquine (PQ)..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/TP/PQ/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg 00-0+3	No. of mice	No. of experiments	Mean control parasite rate %	reated PR% Control PR%
	H 0.1 + PQ 0.1	5		-	98.1 ± 2.6
	H 0.3 + PQ 0.1	5		-	92.2 ± 0.9
N	H 1.0 + PQ 0.1	5	1	-	70.2 ± 5.6
	H 3.0 + PQ 0.1	5		-	0
	Ø	10		20.8	

ED₅₀(range) 0.7(0.2-1.3)

ED₉₀(range) 1.1(0.3-2.0)

Resistance factor I₉₀

	H 0.1 + PQ 0.3	5		-	96.6 ± 2.3
	H 0.3 + PQ 0.3	5		-	82.1 ± 3.5
N	H 1.0 + PQ 0.3	5	1	-	66.3 ± 8.0
	H 3.0 + PQ 0.3	5		-	0.01 ± 0.01
	Ø	10		20.8	

ED₅₀(range) 0.7(0.2-1.3)

ED₉₀(range) 1.2(0.3-2.1)

Resistance factor I₉₀

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 126

COMPOUND NAME Halofantrine (H) +
OR NUMBER Primaquine (PQ)..... PARASITE (SUB)SPECIES *P. berghei*....
FORMULATION ...Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	H 0.1 + PQ 1.0	5		-	100 ± 1.7
	H 0.3 + PQ 1.0	5		-	98.5 ± 2.6
N	H 1.0 + PQ 1.0	5	1	-	66.3 ± 5.4
	H 3.0 + PQ 1.0	5		-	0.1 ± 0.1
	Ø	10		20.8	
ED ₅₀ (range) 0.9(0.6 - 1.3)					
ED ₉₀ (range) 1.5(1.0 - 2.2)					
Resistance factor I ₉₀					
	H 0.1 + PQ 3.0	5		-	94.9 ± 2.1
	H 0.3 + PQ 3.0	5		-	96.3 ± 1.8
N	H 1.0 + PQ 3.0	5	1	-	70.5 ± 9.0
	H 3.0 + PQ 3.0	5		-	0.4 ± 0.4
	Ø	10		20.8	
ED ₅₀ (range) 1.0(0.6 - 1.5)					
ED ₉₀ (range) 1.9(1.2 - 2.9)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 127

COMPOUND NAME Primaquine (PQ) +
OR NUMBER Halofantrine (H)..... PARASITE (SUB)SPECIES P. berghei.....
FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IP/PQ/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR%
	PQ 0.1 + H 0.1	5		-	98.1 ± 2.6
	PQ 0.3 + H 0.1	5		-	96.6 ± 2.3
N	PQ 1.0 + H 0.1	5	1	-	100 ± 1.7
	PQ 3.0 + H 0.1	5		-	94.9 ± 2.1
	Ø	10		20.8	
ED ₅₀ (range) > 3.0					
ED ₉₀ (range) > 3.0					
Resistance factor I ₉₀					
	PQ 0.1 + H 0.3	5		-	92.2 ± 0.9
	PQ 0.3 + H 0.3	5		-	82.1 ± 3.5
N	PQ 1.0 + H 0.3	5	1	-	98.5 ± 2.6
	PQ 3.0 + H 0.3	5		-	96.3 ± 1.8
	Ø	10		20.8	
ED ₅₀ (range) > 3.0					
ED ₉₀ (range) > 3.0					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 128

COMPOUND NAME Primaquine (PQ) +
OR NUMBER Halofantrine (H) PARASITE (SUB)SPECIES P. berghei
FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PQ/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated parasites Control parasites
	PQ 0.1 + H 1.0	5		-	70.2 ± 5.6
	PQ 0.3 + H 1.0	5		-	66.3 ± 8.0
N	PQ 1.0 + H 1.0	5	1	-	66.3 ± 5.4
	PQ 3.0 + H 1.0	5		-	70.5 ± 9.0
	Ø	10		20.8	
ED ₅₀ (range) > 3.0					
ED ₉₀ (range) > 3.0					
Resistance factor I ₉₀					
	PQ 0.1 + H 3.0	5		-	0
	PQ 0.3 + H 3.0	5		-	0.01 ± 0.01
N	PQ 1.0 + H 3.0	5	1	-	0.1 ± 0.1
	PQ 3.0 + H 3.0	5		-	0.4 ± 0.4
	Ø	10		20.8	
ED ₅₀ (range) < 0.1					
ED ₉₀ (range) < 0.1					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZANTOCIDE)

TABLE 129

COMPOUND NAME

OR NUMBER HALOFANTHINE PARASITE (SUB)SPECIES P. falciparum

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 3.0 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PRE Control PRE
	0.1	5		-	80.1 ± 2.3
	0.3	5		-	85.4 ± 2.9
N	1.0	5	1	-	74.9 ± 7.2
	3.0	5		-	0
	5	10		22.5	
ED ₅₀ (range) 0.7 (0.4 - 1.4)					
ED ₉₀ (range) 1.2 (0.7 - 2.2)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 130

COMPOUND NAME

OR NUMBER SULFADIAZINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 2.30 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1	5		-	98.2 ± 2.3
	0.3	5		-	130 ± 11.5
<u>r</u>	1.0	5	1	-	25.1 ± 12.8
	3.0	5		-	0.4 ± 0.2
	0	10		22.5	
ED ₅₀ (range) 0.47(0.3 - 0.8)					
ED ₉₀ (range) 1.1(0.7 - 1.9)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZANTOCIDES)

TABLE 131

COMPOUND NAME HALOFANTRINE +
OR NUMBER SULFADIAZINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION $\text{Twon. 80. H}_2\text{O}$... ROUTE OF ADMINISTRATION : SC/HP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% $\times 100$
	0.1 + 0.1	5		-	91.6 \pm 3.4
	0.3 + 0.1	5		-	85.1 \pm 5.5
N	1.0 + 0.1	5	1	-	41.8 \pm 10.0
	3.0 + 0.1	5		-	0
	\emptyset	10		22.5	
ED ₅₀ (range) 0.5 (0.1 - 1.1)					
ED ₉₀ (range) 0.9 (0.5 - 2.0)					
Resistance factor I ₉₀					
	0.1 + 0.3	5		-	92.8 \pm 4.8
	0.3 + 0.3	5		-	56.0 \pm 17.1
N	1.0 + 0.3	5	1	-	12.4 \pm 7.0
	3.0 + 0.3	5		-	0
	\emptyset	10		22.5	
ED ₅₀ (range) 0.3 (0.2 - 0.6)					
ED ₉₀ (range) 0.7 (0.3 - 1.2)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZANTOCIDES)

TABLE 132

COMPOUND NAME HALOFANTHINE +
OR NUMBER Sulfadiazine..... PARASITE (SUB)SPECIES P. berghei.....
FORMULATION 1.7% w/w / H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR Control PR x 100
	0.1 + 1.0	5		-	30.6 ± 8.5
	0.3 + 1.0	5		-	10.7 ± 4.2
N	1.0 + 1.0	5	1	-	1.3 ± 1.3
	3.0 + 1.0	5		-	0
	\bar{x}	10		22.5	
ED ₅₀ (range) 0.05 (0.02 - 0.1)					
ED ₉₀ (range) 0.2 (0.05 - 0.5)					
Resistance factor I ₉₀					
	0.1 + 3.0	5		-	1.0 ± 1.0
	0.3 + 3.0	5		-	0
N	1.0 + 3.0	5	1	-	0
	3.0 + 3.0	5		-	0
	\bar{x}	10		22.5	
ED ₅₀ (range) 0.02 (0.01 - 0.02)					
ED ₉₀ (range) 0.04 (0.03 - 0.06)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. J. E. J.
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(B) ANTIMONOCIDES

TABLE 133

COMPOUND NAME: SULFADIAZINE +
OR NUMBER: H956620R10..... PARASITE (SUB)SPECIES: *Plasmodium*
FORMULATION: $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_2 \cdot \text{H}_2\text{O}$ ROUTE OF ADMINISTRATION: SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR ₀ Control PR ₀ × 100
	0.1 + 0.1	5		-	31.6 ± 3.4
	0.3 + 0.1	5		-	81.8 ± 4.9
N	1.0 + 0.1	5	1	-	30.6 ± 8.9
	3.0 + 0.1	5		-	1.2 ± 1.0
	2	10		22.5	

ED₅₀(range) 0.45(0.25 - 0.8)

ED₉₀(range) 1.3(0.7 - 2.2)

Resistance factor I₉₀

	0.1 + 0.3	5		-	81.8 ± 4.9
	0.3 + 0.3	5		-	50.0 ± 19.1
N	1.0 + 0.3	5	1	-	1.7 ± 1.0
	3.0 + 0.3	5		-	1.0
	2	10		22.5	

ED₅₀(range) 0.3(0.16 - 0.8)

ED₉₀(range) 0.4(0.3 - 1.0)

Resistance factor I₉₀

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

TABLE 131

COMPOUND NAME SULFADIAZINE

OR NUMBER HALOFANTHINE PARASITE (SUB)SPECIES Plasmodium

FORMULATION Two: 80/H₂O ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 1.0	5		-	41.8 ± 16.0
	0.3 + 1.0	5		-	12.4 ± 7.0
N	1.0 + 1.0	5	1	-	1.3 ± 1.3
	1.0 + 1.0	5		-	0
	0	10		22.5	

ED₅₀(range) 0.1 (0.05 - 0.3)

ED₉₀(range) 0.3 (0.17 - 0.5)

Resistance factor I₉₀

	0.1 + 3.0	5		-	0
	0.3 + 3.0	5		-	0
N	1.0 + 3.0	5		-	0
	3.0 + 3.0	5		-	0
	0	10		22.5	

ED₅₀(range) < 0.1

ED₉₀(range) < 0.1

Resistance factor I₉₀

Chemical Development and Production
Department of Medicine, University of
California, San Francisco, California

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 135

COMPOUND NAME

OR NUMBER .HALOFANTRINE..... PARASITE (SUB)SPECIES .P. berghei.....

FORMULATION ..Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >1.0.. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% X100
	0.1	5		-	97.4 ± 4.0
	0.3	5		-	96.8 ± 3.7
N	0.5	5	1	-	92.2 ± 4.4
	1.0	5		-	24.5 ± 6.2
	Ø	10		23.3	
ED ₅₀ (range) 0.8 (5-12)					
ED ₉₀ (range) 1.5 (11-22)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 136

COMPOUND NAME

OR NUMBER PRIMETHANINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Two 80% H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >0.3.. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.01	5		-	86.5 ± 3.6
	0.03	5		-	79.5 ± 4.1
N	0.1	5	1	-	45.1 ± 4.4
	0.3	5		-	36.3 ± 10.1
	Ø	10		23.3	
ED ₅₀ (range) 0.1 (0.06 - 0.28)					
ED ₉₀ (range) 1.2 (0.6 - 2.8)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 137

COMPOUND NAME HALOFANTRINE +
OR NUMBER PYRIMETHAMINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION Twice 80./H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 0.01	5		-	89.4 ± 1.5
	0.3 + 0.01	5		-	86.7 ± 4.9
N	0.5 + 0.01	5	1	-	35.5 ± 9.5
	1.0 + 0.01	5		-	17.9 ± 6.6
	Ø	10		23.3	
ED ₅₀ (range) 0.46 (0.35 - 0.65)					
ED ₉₀ (range) 0.95 (0.7 - 1.4)					
Resistance factor I ₉₀					
	0.1 + 0.03	5		-	90.0 ± 7.6
	0.3 + 0.03	5		-	81.0 ± 5.2
N,	0.5 + 0.03	5	1	-	73.4 ± 9.1
	1.0 + 0.03	5		-	29.8 ± 8.2
	Ø	10		23.3	
ED ₅₀ (range) 0.58 (0.23 - 1.7)					
ED ₉₀ (range) 1.8 (0.73 - 3.5)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 135

COMPOUND NAME HALOFANTRINE +
OR NUMBER PYRIMETHAMINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 0.1	5		-	69.8 ± 6.3
	0.3 + 0.1	5		-	63.0 ± 3.3
N	0.5 + 0.1	5	1	-	41.5 ± 1.6
	1.0 + 0.1	5		-	29.5 ± 12.3
	Ø	10		23.3	
ED ₅₀ (range) 0.4 (0.25 - 0.72)					
ED ₉₀ (range) 2.6 (1.5 - 5.0)					
Resistance factor I ₉₀					
	0.1 + 0.3	5		-	47.4 ± 1.9
	0.3 + 0.3	5		-	18.0 ± 4.4
N	0.5 + 0.3	5	1	-	4.5 ± 2.5
	1.0 + 0.3	5		-	1.1 ± 0.5
	Ø	10		23.3	
ED ₅₀ (range) 0.4 (0.14 - 0.72)					
ED ₉₀ (range) 0.4 (0.15 - 0.72)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 139

COMPOUND NAME PYRIMETHAMINE +
OR NUMBER HALOFANTHINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80 / H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.01 + 0.1	5		-	89.4 ± 1.5
	0.03 + 0.1	5		-	90.0 ± 7.6
N	0.1 + 0.1	5	1	-	69.8 ± 6.3
	0.3 + 0.1	5		-	47.7 ± 1.5
	Ø	10		23.3	
ED ₅₀ (range) 0.25 (0.16 - 0.4)					
ED ₉₀ (range) 2 ± 1.5 - 4					
Resistance factor I ₉₀					
	0.01 + 0.3	5		-	86.7 ± 4.9
	0.03 + 0.3	5		-	81.0 ± 5.2
N	0.1 + 0.3	5	1	-	63.0 ± 3.2
	0.3 + 0.3	5		-	18.9 ± 7.7
	Ø	10		23.3	
ED ₅₀ (range) 0.11 (0.05 - 0.16)					
ED ₉₀ (range) 0.42 (0.3 - 0.6)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 140

COMPOUND NAME PYRIMETHAMINE +
OR NUMBER HALOFANTHINE..... PARASITE (SUB)SPECIES ...*P. berghei*.....
FORMULATION $\text{Twinn 80, H}_2\text{O}$... ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.01 + 0.5	5		-	35.5 ± 9.5
	0.03 + 0.5	5		-	73.4 ± 9.1
N	0.1 + 0.5	5	1	-	41.3 ± 10.6
	0.3 + 0.5	5		-	4.3 ± 2.5
	Ø	10		23.3	
ED ₅₀ (range) 0.02 (0.01 - 0.1)					
ED ₉₀ (range) 0.23 (0.14 - 0.36)					
Resistance factor I ₉₀					
	0.01 + 1.0	5		-	17.9 ± 6.6
	0.03 + 1.0	5		-	29.8 ± 8.2
N	0.1 + 1.0	5	1	-	29.5 ± 12.3
	0.3 + 1.0	5		-	1.9 ± 0.8
	Ø	10		23.3	
ED ₅₀ (range) 0.02 (0.01 - 0.08)					
ED ₉₀ (range) 0.11 (0.05 - 0.35)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 141

COMPOUND NAME

OR NUMBER HALOFANTRINE..... PARASITE (SUB)SPECIES *P. falciparum*.....

FORMULATION 250.0 mg/kg H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 250.0 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.1	5		-	84.8 ± 4.6
	0.3	5		-	72.1 ± 4.7
N	0.5	5	1	-	63.1 ± 9.6
	1.0	5		-	48.3 ± 5.3
	∅	10		23.7	
ED ₅₀ (range) 0.5 (0.3 - 1.1)					
ED ₉₀ (range) 3.4 (2.1 - 7.4)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 142

COMPOUND NAME

OR NUMBER ..MINOXYPHINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Twiss. SC / H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 2.30... MG/KG X 4L.

Strain	Daily dose mg/kg DO-0+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% X100
	1.0	5		-	80.0 ± 3.3
	3.0	5		-	66.1 ± 5.0
N	10.0	5	1	-	40.5 ± 15.0
	30.0	5		-	22.4 ± 7.5
	Ø	10		23.7	
ED ₅₀ (range) 5.4(2.7-12.5)					
ED ₉₀ (range) 70.0(28.0-135)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 143

COMPOUND NAME HALOFANTRINE +
OR NUMBER MINOCYCLINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION *Two 0.5% H₂O* ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR ₂ Control PR ₂ x 100
	0.1 + 1.0	5		-	88.0 ± 4.1
	0.3 + 1.0	5		-	69.5 ± 3.3
N	0.5 + 1.0	5	1	-	62.4 ± 4.1
	1.0 + 1.0	5		-	43.0 ± 3.3
	0	10		23.7	
ED ₅₀ (range) 0.45 (0.27-1.0)					
ED ₉₀ (range) 2.3 (1.4-5.1)					
Resistance factor I ₉₀					
	0.1 + 3.0	5		-	88.8 ± 4.1
	0.3 + 3.0	5		-	80.4 ± 4.0
N	0.5 + 3.0	5	1	-	69.8 ± 6.0
	1.0 + 3.0	5		-	37.1 ± 5.1
	0	10		23.7	
ED ₅₀ (range) 0.48 (0.24-1.0)					
ED ₉₀ (range) 1.7 (0.8-3.5)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 111

COMPOUND NAME HALOFANTRINE +
OR NUMBER MINGSHICHINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% $\times 100$
	0.1 + 10.0	5		-	92.0 \pm 2.0
	0.3 + 10.0	5		-	79.5 \pm 1.5
N	0.5 + 10.0	5	1	-	45.0 \pm 1.0
	1.0 + 10.0	5		-	35.0 \pm 2.0
	Ø	10		23.7	
ED ₅₀ (range) 0.45(0.26-0.95)					
ED ₉₀ (range) 2.1(1.2-4.2)					
Resistance factor I ₉₀					
	0.1 + 30.0	5		-	27.6 \pm 9.4
	0.3 + 30.0	5		-	12.3 \pm 5.4
N	0.5 + 30.0	5	1	-	4.2 \pm 1.0
	1.0 + 30.0	5		-	0.7 \pm 0.4
	Ø	10		23.7	
ED ₅₀ (range) 0.05(0.03-0.1)					
ED ₉₀ (range) 0.25(0.15-0.45)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 145

COMPOUND NAME MINOCYCLINE +
OR NUMBER HALOFANTRINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION $\text{Twice } 80 / \text{H}_2\text{O}$ ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% $\times 100$
	1.0 + 0.1	5		-	80.0 \pm 2.3
	3.0 + 0.1	5		-	85.8 \pm 1.1
N	10.0 + 0.1	5	1	-	84.0 \pm 2.1
	30.0 + 0.1	5		-	24.5 \pm 1.2
	\emptyset	10		25.7	
ED ₅₀ (range) 13.0 (2.7 - 44)					
ED ₉₀ (range) 64.0 (13.0 - 215)					
Resistance factor I ₉₀					
	1.0 + 0.3	5		-	60.5 \pm 1.1
	3.0 + 0.3	5		-	80.4 \pm 1.1
N	10.0 + 0.3	5	1	-	74.5 \pm 2.1
	30.0 + 0.3	5		-	12.5 \pm 2.4
	\emptyset	10		25.7	
ED ₅₀ (range) 8.3 (1.4 - 27.0)					
ED ₉₀ (range) 33.0 (5.7 - 105)					
Resistance factor I ₉₀					

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Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR%
	10.0 + 0.5	5			4.5 ± 1.1
	30.0 + 0.5	5			5.7 ± 1.5
N	10.0 + 0.5	5	1		4.5 ± 1.1
	30.0 + 0.5	5			4.5 ± 1.1
	0	10		23.4	
ED ₅₀ (range) 3.8(1.1 - 9.4)					
ED ₉₀ (range) 17.0(5.0 - 41.0)					
Resistance factor I ₉₀					
	10.0 + 1.0	5			4.5 ± 1.1
	30.0 + 1.0	5			5.7 ± 1.5
N	10.0 + 1.0	5	1		4.5 ± 1.1
	30.0 + 1.0	5			5.7 ± 1.5
	0	10		23.4	
ED ₅₀ (range) 2.0(0.8 - 7.1)					
ED ₉₀ (range) 8.0(3.0 - 28.0)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTAIDES)

TABLE 111

COMPOUND NAME

OR NUMBER

HEC-1, FIDANTHIL, etc.

PARASITE (SUB)SPECIES *P. falciparum*

FORMULATION *Two 80/H₂O* ROUTE OF ADMINISTRATION: SC/*intraperitoneal*

MAY. MUM TOLERATED DOSE (MTD) *> 1.0* MG/KG X *5*

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PPE Control PPE
	0.1	5			
	0.3	5			
N	0.5	5	1		
	1.0	5			
	<i>2</i>	10		27.0	
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL ACTIVITY
(BIOASSAY METHOD)

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COMPOUND NAME:

OR NUMBER: 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11.1

Strain	Daily dose mg/kg DG-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated vs. Control %
	C1 + IC	5			100
	C3 + IC	5			100
N	C5 + IC	5	1		100
	C6 + IC	5			100
	C7	5			100

[illegible]

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

TABLE 10,1

COMPOUND NAME: *Chloroquine*

OR NUMBER: *1000* PARASITE (SUB SPECIES): *Plasmodium falciparum*

FORMULATION: *0.5% w/v* ROUTE OF ADMINISTRATION: *SCIP/PO/IV*

MAXIMUM TOLERATED DOSE (MTD): *100* MG/KG X *1*

Strain	Daily dose mg/kg DO-G+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PPE Control PPE %
<i>100</i>	<i>10</i>	<i>10</i>			
<i>100</i>	<i>20</i>	<i>10</i>			
<i>100</i>	<i>40</i>	<i>10</i>			
<i>100</i>	<i>80</i>	<i>10</i>			
<i>100</i>	<i>100</i>	<i>10</i>			
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					
<i>100</i>	<i>10</i>	<i>10</i>			
<i>100</i>	<i>20</i>	<i>10</i>			
<i>100</i>	<i>40</i>	<i>10</i>			
<i>100</i>	<i>80</i>	<i>10</i>			
<i>100</i>	<i>100</i>	<i>10</i>			
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

Table 151

COMPOUND NAME CLINDAMICIN +

DR NUMBER HALOANTHRIN-95 PARASITE SUB SPECIES P. falciparum

FORMULATION 1.25% SC / H₂O ROUTE OF ADMINISTRATION : SCAP-PO-IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PRE Control PRE
	10 + C1	5		-	9.1 ± 1.1
	30 + C1	5		-	1.1 ± 1.1
N	100 + C1	5	1	-	3.1 ± 1.1
	300 + C1	5		-	1.3 ± 1.1
	Ø	10		24.0	
ED ₅₀ (range) 1.1 - 1.1					
ED ₉₀ (range) 1.1 - 1.1					
Resistance factor I ₉₀					
	10 + C3	5		-	10.0 ± 1.1
	30 + C3	5		-	10.0 ± 1.1
N	100 + C3	5	1	-	10.0 ± 1.1
	500 + C3	5		-	1.3 ± 1.1
	Ø	10		27.0	
ED ₅₀ (range) 1.1 - 1.1					
ED ₉₀ (range) 1.1 - 1.1					
Resistance factor I ₉₀					

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Figure 1. The study area.

TABLE 15-3

OR NUMBER HUC6709 PARASITE (SUB)SPECIES A. A. 1

FORMULATION : Two 50/1/1, C... ROUTE OF ADMINISTRATION : SC ~~10/10/10~~

MAXIMUM TOLERATED DOSE (MTD) 2100 MG/KG X 4

[illegible]

174

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 1.5.1

COMPOUND NAME

OR NUMBER TETRAHYDRO-4-CHLORO-1-METHYLPYRIMIDIN-2(1H)-ONE PARASITE (SUB)SPECIES P. falciparum

FORMULATION 100 mg/kg ROUTE OF ADMINISTRATION : SC/ID/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 300 MG/KG x 4 d.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR ₁₀₀ Control PR ₁₀₀
	10	5		-	100
	30	5		-	100
N	100	5	1	-	100
	300	5		-	100
	2	5		100	
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 155

COMPOUND NAME HALOFANTHINE +

OR NUMBER TELITHIOCYANINE..... PARASITE (SUB)SPECIES P. falciparum.....

FORMULATION 100% S.C. / H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.1 + 1.0	5		-	50.7 ± 4.2
	0.3 + 1.0	5		-	51.1 ± 4.5
N	0.5 + 1.0	5	1	-	39.2 ± 4.0
	1.0 + 1.0	5		-	34.3 ± 3.0
	✓	10		26.6	
ED ₅₀ (range) 0.1 - 1.0					
ED ₉₀ (range) 0.3 - 1.0					
Resistance factor I ₉₀					
	0.1 + 3.0	5		-	75.3 ± 2.1
	0.3 + 3.0	5		-	69.5 ± 4.1
N	0.5 + 3.0	5	1	-	52.9 ± 5.4
	1.0 + 3.0	5		-	48.0 ± 2.5
	✓	10		26.6	
ED ₅₀ (range) 0.1 - 3.0					
ED ₉₀ (range) 0.3 - 3.0					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 156

COMPOUND NAME HALOFANTRINE +

OR NUMBER TETRACYCLINE..... PARASITE (SUB)SPECIES P. falciparum.....

FORMULATION T. 1000.80 / H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.1 + 10.0	5		-	73.6 ± 2.0
	0.3 + 10.0	5		-	44.7 ± 1.0
N	0.5 + 10.0	5	1	-	42.5 ± 2.4
	1.0 + 10.0	5		-	31.7 ± 3.4
	Ø	10		26.6	
ED ₅₀ (range) 0.5 (0.1 - 1.2)					
ED ₉₀ (range) 1.35 (1.0 - 3.2)					
Resistance factor I ₉₀					
	0.1 + 30.0	5		-	75.1 ± 2.3
	0.3 + 30.0	5		-	56.0 ± 5.3
N	0.5 + 30.0	5	1	-	40.2 ± 4.4
	1.0 + 30.0	5		-	35.2 ± 3.0
	Ø	10		26.6	
ED ₅₀ (range) 0.6 (0.3 - 1.5)					
ED ₉₀ (range) 1.35 (1.0 - 3.2)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 157

COMPOUND NAME TETRACYCLINE +

OR NUMBER ..HALOFANTRINE..... PARASITE (SUB)SPECIES ..P. vivax.....

FORMULATION ~~Tween 80~~/H₂O. ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	1.0 + 0.1	5		-	80.7 ± 4.2
	3.0 + 0.1	5		-	75.3 ± 2.1
N	10.0 + 0.1	5	1	-	73.6 ± 2.0
	30.0 + 0.1	5		-	75.1 ± 2.3
	0	10		26.6	
ED ₅₀ (range) > 30					
ED ₉₀ (range) > 30					
Resistance factor I ₉₀					
	1.0 + 0.3	5		-	51.1 ± 4.5
	3.0 + 0.3	5		-	69.5 ± 4.1
N	10.0 + 0.3	5	1	-	44.9 ± 3.0
	30.0 + 0.3	5		-	56.0 ± 5.3
	0	10		26.6	
ED ₅₀ (range) 18.0 (5.2 - 47.0)					
ED ₉₀ (range) 15.5 (4.0 - 40.0)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 158

COMPOUND NAME TETRACYCLINE +
OR NUMBER HALOFANTINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	1.0 + 0.5	5		-	39.2 ± 4.9
	3.0 + 0.5	5		-	52.9 ± 5.9
N	10.0 + 0.5	5	1	-	40.5 ± 3.4
	30.0 + 0.5	5		-	40.2 ± 4.4
	Ø	10		26.6	
ED ₅₀ (range)					
ED ₉₀ (range) > 30					
Resistance factor I ₉₀					
	1.0 + 1.0	5		-	34.3 ± 3.0
	3.0 + 1.0	5		-	48.0 ± 2.5
N	10.0 + 1.0	5	1	-	31.7 ± 3.7
	30.0 + 1.0	5		-	35.2 ± 3.0
	Ø	10		26.6	
ED ₅₀ (range)					
ED ₉₀ (range) > 30					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

3. J. C. SUTHERLAND, *ibid.* 1961, 1962.

TABLE 159

COMPOUND NAME

OR NUMBER FLOPPING PARASITE (SUB)SPECIES F. floppus

FORMULATION : $\text{TiSO}_4/\text{H}_2\text{O}$ ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 2.5.0. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PRT Control PRT x 100
	0.1	5		-	83.4 ± 4.9
	0.2	5		-	70.4 ± 5.1
N	0.2	5		-	46.6 ± 7.8
	1.0	5		-	4.2 ± 3.9
	3.0	5		-	0.02 ± 0.01
	7	10		25.3	
ED ₅₀ (range) 0.3(0.2-0.5)					
ED ₉₀ (range) 0.4(0.4-1.2)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

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MAXIMUM TOLERATED DOSE (MTD) ~ 600 MG/KG X 4.

Principal Investigator: Professor W. Peters
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London School of Hygiene & Tropical Medicine

• TABLE 61

OR NUMBER Quinine..... PARASITE (SUB)SPECIES T. trachy.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/~~IP~~^F/~~PO~~^Q

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

S. 100-101-102

COMPOUND NAME: FLOXAPYRONE

GR. NUMBER: 100-101-102 PARASITE (SUBSTRATE): F. (F. vivax)

FORMULATION: 100% S.S. / H₂O ROUTE OF ADMINISTRATION: S.C. + P.O.

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated / Control TP ₅₀ %
	0.1 + 30.0	5		-	80.0 ± 2.2
	0.3 + 30.0	5		-	54.4 ± 13.9
N	0.5 + 30.0	5	1	-	27.1 ± 15.9
	1.0 + 30.0	5		-	0.4 ± 0.0
	3.0 + 30.0	5		-	0
	✓	10		25.3	

ED₅₀(range) 0.2 (0.1 - 0.4)ED₉₀(range) 0.5 (0.3 - 1.0)Resistance factor I₉₀

	0.1 + 100.0	5		-	8.2 ± 3.0
	0.3 + 100.0	5		-	5.8 ± 1.4
N	0.5 + 100.0	5	1	-	4.1 ± 1.5
	1.0 + 100.0	5		-	0
	3.0 + 100.0	5		-	0
	0	10		25.3	

ED₅₀(range) 0.05 (0.03 - 0.1)ED₉₀(range) 0.1 (0.04 - 0.4)Resistance factor I₉₀

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOCK SUBSTITUTED)

TABLE 163

COMPOUND NAME QUININE +
OR NUMBER FLEXABURONE PARASITE (SUB)SPECIES P. berghei
FORMULATION 100.0% H₂O ROUTE OF ADMINISTRATION : SC/IV/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PPS Control PPS
	3.0 + 0.1	5		-	88.0 ± 4.4
	10.0 + 0.1	5		-	81.3 ± 2.9
N	30.0 + 0.1	5	1	-	80.0 ± 2.2
	100.0 + 0.1	5		-	82 ± 3.0
	∅	10		25.3	
ED ₅₀ (range) 35.0(25.0 - 60.0)					
ED ₉₀ (range) 90.0(61.0 - 150)					
Resistance factor I ₉₀					
	3.0 + 0.3	5		-	82.7 ± 2.3
	10.0 + 0.3	5		-	73.8 ± 7.7
N	30.0 + 0.3	5	1	-	84.4 ± 13.1
	100.0 + 0.3	5		-	85 ± 1.4
	∅	10		25.3	
ED ₅₀ (range) 17.0(7.1 - 50.0)					
ED ₉₀ (range) 70.0(30.0 - 200)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL RESULTS

- TABLE 16.1

(BY ROUTE OF ADMINISTRATION)

COMPOUND NAME QUININE +OR NUMBER EXPERIMENTAL PARASITE (SUB-RECEIVED) F. longiFORMULATION Twice 800 mg H₂O ROUTE OF ADMINISTRATION: SC 400 mg

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated / Control parasite rate %
	3.0 + 0.5	5		-	51.8 ± 15.3
	10.0 + 0.5	5		-	50.2 ± 16.2
N	30.0 + 0.5	5	1	-	25.0 ± 15.3
	100.0 + 0.5	5		-	4.1 ± 1.8
	0	5		25.3	
ED ₅₀ (range) 11.5 (7.5 - 20.0)					
ED ₉₀ (range) 50.0 (40.0 - 100)					
Resistance factor I ₉₀					
	3.0 + 1.0	5		-	0.7 ± 0.2
	10.0 + 1.0	5		-	0.05 ± 0.05
N	30.0 + 1.0	5	1	-	0.4 ± 0.2
	100.0 + 1.0	5		-	0
	0	10		25.3	
ED ₅₀ (range) 0.2 (0.1 - 0.4)					
ED ₉₀ (range) 1.5 (0.5 - 3.2)					
Resistance factor I ₉₀					

Principal Investigator: Professor A. Peters
 Department of Medical Protozoology,
 London School of Hygiene & Tropical Medicine

Chemical Name

Chemical Name

OR NUMBER ... C.N.S. 400000000 ...

Formulation ... $\text{C}_{10}\text{H}_{16}\text{O}_2$... Route of Administration ...

Maximum Tolerated Dose (MTD) ≥ 10 mg/kg x 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate \pm S.E.	Treat. group parasite rate \pm S.E.
	0.3	5			0.00 \pm 0.00
	1.0	5			0.00 \pm 0.00
IN	3.0	5	1		0.00 \pm 0.00
	5.0	5			0.00 \pm 0.00
	10.0	5			0.00 \pm 0.00
	20.0	5			0.00 \pm 0.00

ED₅₀ (range) ...

ED₉₀ (range) ...

Resistance factor 10_5

ED₅₀ (range)

ED₉₀ (range)

Resistance factor 10_5

... of ...

... of ...

... of ...

DATE: 10/1/54

MEMORANDUM FOR: FLOWERS, R. H.

FROM: CHASE, R. H.

SUBJECT: 100% FLOWERS

FORMULATION: 100% FLOWERS

MAXIMUM TOLERATED DOSE (MTD): 100% FLOWERS

Strain	Daily Dose mg/kg DD-D+3	No. of mice	No. of experiments	Mean Control parasite rate	Tested / 100%
	0.1 + 0.3	5			50.0 ± 10.0
	0.3 + 0.3	5			40.0 ± 10.0
P ₁	0.5 + 0.3	5	1		30.0 ± 10.0
	0.7 + 0.3	5			20.0 ± 10.0
	0.9 + 0.3	5			10.0 ± 10.0
	1.1	5			0.0 ± 10.0

100% range: 0.1 + 0.3

50% range: 0.1 + 0.3

Assistance factor 100

	0.1 + 0.3	5			20.0 ± 10.0
	0.3 + 0.3	5			30.0 ± 10.0
P ₁	0.5 + 0.3	5	1		10.0 ± 10.0
	0.7 + 0.3	5			0.0 ± 10.0
	0.9 + 0.3	5			0.0 ± 10.0
	1.1	5			0.0 ± 10.0

100% range

50% range

Assistance factor 100

100% range: 0.1 + 0.3
50% range: 0.1 + 0.3
Assistance factor 100

NAME OF NAME: FLEX SCALING +

NAME OF NAME: S.M.S. SCALING + NAME OF NAME: PARASITE SUBSTRATE: *Plasmodium*FORMULATION: Tricloro. 80% H_2O ROUTE OF ADMINISTRATION: SC/IT

MAXIMUM TOLERATED DOSE (MTD) (MG/KG X DAY)

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PPT Control PPT
	0.1 + 3.0	5		-	25.5 ± 4.5
	0.3 + 3.0	5		-	24.5 ± 2.4
N	0.5 + 3.0	5	1	-	3.4 ± 2.0
	1.0 + 3.0	5		-	0.02 ± 0.01
	3.0 + 3.0	5		-	0
	0	10		25.3	
ED ₅₀ (range) 0.03(0.01-0.2)					
ED ₉₀ (range) 0.2(0.1-0.5)					
Resistance factor I ₉₀					
	0.1 + 5.0	5		-	25.3 ± 4.5
	0.3 + 5.0	5		-	19.0 ± 0.4
N	0.5 + 5.0	5	1	-	1.2 ± 0.5
	1.0 + 5.0	5		-	0.02 ± 0.01
	3.0 + 5.0	5		-	0
	0	10		25.3	
ED ₅₀ (range) 0.1(0.06-0.2)					
ED ₉₀ (range) 0.2(0.1-0.4)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peter
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 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

- Jan 1969

TABLE 1. CHLOROQUINE

COMPOUND NAME CHLOROQUINE +

DR NUMBER ~~FL-100-101~~ PARASITE (SUB)SPECIES *P. berghei*FORMULATION ~~Tween 80~~ / H₂O ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.3 + 0.1	5		-	52.6 ± 1.5
	1.0 + 0.1	5		-	35.8 ± 3.1
N	3.0 + 0.1	5	1	-	25.5 ± 4.5
	5.0 + 0.1	5		-	25.3 ± 4.8
	Ø	10		25.3	
ED ₅₀ (range) 0.3 (0.2 - 0.5)					
ED ₉₀ (range) 21.0 (11.0 - 48.0)					
Resistance factor I ₉₀					
	0.3 + 0.3	5		-	45.8 ± 3.7
	1.0 + 0.3	5		-	30.8 ± 3.3
N	3.0 + 0.3	5	1	-	24.0 ± 2.4
	5.0 + 0.3	5		-	18.0 ± 4.4
	Ø	10		25.3	
ED ₅₀ (range) 0.3 (0.2 - 0.5)					
ED ₉₀ (range) 0.3 - 1.4					
Resistance factor I ₉₀					

Principal Investigator: Professor W. J. E. M.
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OR NUMBER 100-100000000 100-100000000 100-100000000 100-100000000 100-100000000

FORMULATION ... Tween 80 4.2% ...

MAXIMUM TOLERATED DOSE (MTD) mg/kg/day

Journal of Tropical Medicine and Hygiene
 Journal of Tropical Geography
 Journal of Tropical Medicine

AD-A185 118

CHEMOTHERAPY OF RODENT MALARIA(U) LONDON SCHOOL OF
HYGIENE AND TROPICAL MEDICINE (ENGLAND) DEPT OF MEDICAL
PROTOZOOLOGY W PETERS JUL 85 DAND17-84-C-4018

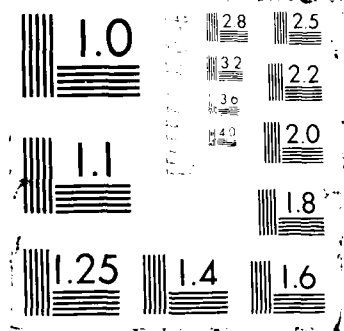
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 171

COMPOUND NAME FLOXACRINE

OR NUMBER ..H.V.1528..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80./H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >100.. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1	5		-	95.5 ± 5.7
	0.3	5		-	90.0 ± 2.9
N	0.5	5	1	-	43.6 ± 14.3
	1.0	5		-	0.3 ± 0.3
	∅	10		22.5	
ED ₅₀ (range) 0.44 (0.31 - 0.52)		Isobolar Unit			
ED ₉₀ (range) 0.64 (0.46 - 0.8)					
Resistance factor I ₉₀ 1.0					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 17.2

COMPOUND NAME

OR NUMBER TETRACYCLINE..... PARASITE (SUB SPECIES) P. berghei.....

FORMULATION Tween 30/H₂O... ROUTE OF ADMINISTRATION : SC/12-14

MAXIMUM TOLERATED DOSE (MTD) >100.0 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% $\times 100$
	3.0	5		-	95.4 \pm 2.3
	10.0	5		-	78.4 \pm 8.7
N	30.0	5	1	-	53.7 \pm 10.9
	100.0	5		-	4.3 \pm 2.0
	\emptyset	10		22.5	
ED ₅₀ (range) 20.0 (12.0 - 42.0)		Isobolar Unit			
ED ₉₀ (range) 67.0 (41.0 - 140)					
Resistance factor I ₉₀ 1.0					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 173

COMPOUND NAME FLOXAURINE +

OR NUMBER TETRALYCHNE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 3.0	5		-	95.6 ± 3.1
	0.3 + 3.0	5		-	57.6 ± 10.0
N	0.5 + 3.0	5	1	-	15.6 ± 6.7
	1.0 + 3.0	5		-	0
	Ø	10		22.5	
ED ₅₀ (range) 0.23(0.17 - 0.37)		Isobolar Units			
ED ₉₀ (range) 0.38(0.27 - 0.6)					
Resistance factor I ₉₀ 0.59					
	0.1 + 10.0	5		-	88.4 ± 3.2
	0.3 + 10.0	5		-	60.2 ± 4.4
N	0.5 + 10.0	5	1	-	1.9 ± 1.9
	1.0 + 10.0	5		-	0
	Ø	10		22.5	
ED ₅₀ (range) 0.22(0.14 - 0.35)		Isobolar Units			
ED ₉₀ (range) 0.36(0.24 - 0.58)					
Resistance factor I ₉₀ 0.56					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 171

COMPOUND NAME FLOXACRINE +
OR NUMBER TETRACYCLINE..... PARASITE (SUB)SPECIES ...*P. berghei*....
FORMULATION ...Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 30.0	5		-	51.6 ± 10.4
	0.3 + 30.0	5		-	28.2 ± 7.0
N	0.5 + 30.0	5	1	-	2.6 ± 1.7
	1.0 + 30.0	5		-	0
	Ø	10		22.5	
ED ₅₀ (range) 0.17 (<0.1 - 0.26)		Isobolar Units			
ED ₉₀ (range) 0.3 (0.16 - 0.46)					
Resistance factor I ₉₀ 0.46					
	0.1 + 100.0	5		-	4.3 ± 1.6
	0.3 + 100.0	5		-	3.5 ± 0.6
N	0.5 + 100.0	5	1	-	0.3 ± 0.3
	1.0 + 100.0	5		-	0
	Ø	10		22.5	
ED ₅₀ (range) 0.03 (0.02 - 0.05)		Isobolar Units			
ED ₉₀ (range) 0.1 (0.05 - 0.19)					
Resistance factor I ₉₀ 0.16					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 175

COMPOUND NAME TETRACYCLINE +

OR NUMBER FLOXALINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80 / H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	3.0 + 0.1	5		-	95.6 ± 3.1
	10.0 + 0.1	5		-	88.4 ± 3.2
N	30.0 + 0.1	5	1	-	51.6 ± 10.4
	100.0 + 0.1	5		-	4.3 ± 1.6
	Ø	10		22.5	
ED ₅₀ (range) 22.0(12.0 - 40.0)		Isobolar Units			
ED ₉₀ (range) 80.0(44.0 - 140)					
Resistance factor I ₉₀ 1.2					
	3.0 + 0.3	5		-	57.6 ± 10.0
	10.0 + 0.3	5		-	60.2 ± 4.4
N	30.0 + 0.3	5	1	-	28.2 ± 7.0
	100.0 + 0.3	5		-	3.5 ± 0.6
	Ø	10		22.5	
ED ₅₀ (range) 7.5(2.7 - 18.0)		Isobolar Units			
ED ₉₀ (range) 39.0(14.0 - 95.0)					
Resistance factor I ₉₀ 0.58					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 176

COMPOUND NAME TETRACYCLINE +

OR NUMBER FLUXALINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/TP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	3.0 + 0.5	5		-	15.6 ± 6.7
	10.0 + 0.5	5		-	11.9 ± 1.9
N	30.0 + 0.5	5	1	-	2.6 ± 1.7
	100.0 + 0.5	5		-	0.3 ± 0.3
	∅	10		22.5	
ED ₅₀ (range) 0.95 (0.3 - 2.0)		Isobolar Units			
ED ₉₀ (range) 0.9 (2.2 - 14.0)					
Resistance factor I ₉₀ 0.1					
	3.0 + 1.0	5		-	0
	10.0 + 1.0	5		-	0
N	30.0 + 1.0	5	1	-	0
	100.0 + 1.0	5		-	0
	∅	10		22.5	
ED ₅₀ (range) < 3.0		Isobolar Units			
ED ₉₀ (range) < 3.0					
Resistance factor I ₉₀ < 0.04					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 177

COMPOUND NAME

OR NUMBER ..FLOXARINE..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ≥1:0... MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% × 100
	0.1	5		-	95.5 ± 5.7
	0.3	5		-	90.0 ± 2.9
N	0.5	5	1	-	43.6 ± 14.3
	1.0	5		-	0.3 ± 0.3
	0	10		22.5	
ED ₅₀ (range) 0.44(0.31 - 0.52)		Isobolar Unit			
ED ₉₀ (range) 0.64(0.46 - 0.8)					
Resistance factor I ₉₀ 1.0					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 178

COMPOUND NAME

OR NUMBER ERYTHROMYCIN..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/HP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 600.0 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	30.0	5		-	91.6 ± 1.5
	100.0	5		-	70.4 ± 14.7
N	300.0	5	1	-	49.2 ± 9.6
	600.0	5		-	14.8 ± 8.2
	Ø	10		22.5	
ED ₅₀ (range) 190(113 - 370)		Isobolar Unit			
ED ₉₀ (range) 950(560 - 1850)					
Resistance factor I ₉₀ 1.0					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 170

COMPOUND NAME FLOXALINE +

OR NUMBER ERYTHROMYCIN PARASITE (SUB)SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.1 + 30.0	5		-	82.4 ± 6.7
	0.3 + 30.0	5		-	77.4 ± 7.9
N	0.5 + 30.0	5	1	-	22.1 ± 14.2
	1.0 + 30.0	5		-	0
	Ø	10		22.5	
ED ₅₀ (range) 0.23(0.13 - 0.43)					
ED ₉₀ (range) 0.38(0.21 - 0.7)					
Resistance factor I ₉₀ 0.59 Isobolar Units					
	0.1 + 100.0	5		-	79.1 ± 6.3
	0.3 + 100.0	5		-	69.2 ± 4.4
N	0.5 + 100.0	5	1	-	4.5 ± 1.6
	1.0 + 100.0	5		-	0
	Ø	10		22.5	
ED ₅₀ (range) 0.22(0.13 - 0.32)					
ED ₉₀ (range) 0.36(0.21 - 0.53)					
Resistance factor I ₉₀ 0.56 Isobolar Units					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 180

COMPOUND NAME FLOXACRINE +

OR NUMBER ERYTHROMYCIN..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{X100}
	0.1 + 300.0	5		-	48.8 ± 14.2
	0.3 + 300.0	5		-	24.7 ± 9.1
N	0.5 + 300.0	5	1	-	2.0 ± 0.9
	1.0 + 300.0	5		-	0
	∅	10		22.5	
ED ₅₀ (range) 0.12(0.08 - 0.23)		Isobolar Units			
ED ₉₀ (range) 0.24(0.16 - 0.46)					
Resistance factor I ₉₀ 0.38					
	0.1 + 600.0	5		-	18.4 ± 6.1
	0.3 + 600.0	5		-	3.3 ± 2.2
N	0.5 + 600.0	5	1	-	1.3 ± 1.2
	1.0 + 600.0	5		-	0
	∅	10		22.5	
ED ₅₀ (range) 0.06(0.04 - 0.12)		Isobolar Units			
ED ₉₀ (range) 0.16(0.11 - 0.3)					
Resistance factor I ₉₀ 0.25					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 181

COMPOUND NAME ERYTHROMYCIN +

OR NUMBER FLOXALURINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION ...Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	30.0 + 0.1	5		-	82.4 ± 6.7
	100.0 + 0.1	5		-	79.1 ± 6.3
N	300.0 + 0.1	5	1	-	48.8 ± 14.2
	600.0 + 0.1	5		-	18.4 ± 6.1
	∅	10		22.5	
ED ₅₀ (range) 155(76.0 - 460)		Isobolar Units			
ED ₉₀ (range) 930(450 - 2700)					
Resistance factor I ₉₀ 0.98					
	30.0 + 0.3	5		-	77.4 ± 7.9
	100.0 + 0.3	5		-	69.2 ± 4.4
N	300.0 + 0.3	5	1	-	24.7 ± 9.1
	600.0 + 0.3	5		-	3.3 ± 2.2
	∅	10		22.5	
ED ₅₀ (range) 95.0(50.0 - 195)		Isobolar Units			
ED ₉₀ (range) 400(205 - 800)					
Resistance factor I ₉₀ 0.42					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 192

COMPOUND NAME ERYTHROMYCIN +

OR NUMBER FLOXACRINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	30.0 + 0.5	5		-	22.1 ± 14.2
	100.0 + 0.5	5		-	4.5 ± 1.6
N	300.0 + 0.5	5	1	-	2.0 ± 0.9
	600.0 + 0.5	5		-	1.3 ± 1.2
	∅	10		22.5	
ED ₅₀ (range) 7.5(3.5 - 19.0)		Isobolar Units			
ED ₉₀ (range) 70.0(33.0 - 130)					
Resistance factor I ₉₀ 0.07					
	30.0 + 1.0	5		-	0
	100.0 + 1.0	5		-	0
N	300.0 + 1.0	5	1	-	0
	600.0 + 1.0	5		-	0
	∅	10		22.5	
ED ₅₀ (range) < 30		Isobolar Units			
ED ₉₀ (range) < 30					
Resistance factor I ₉₀ <0.03					

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SUMMARY OF ANTIMALARIAL DRUG TESTS

-TABLE 183

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME

OR NUMBER ... FLOXACRINE..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80.1.H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ..>1:0.. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ¹⁰⁰
	0.1	5		-	80.4 ± 2.3
	0.3	5		-	64.5 ± 5.1
N	0.5	5	1	-	28.3 ± 8.7
	1.0	5		-	1.0 ± 0.5
	Ø	10		35.7	
ED ₅₀ (range) 0.25(0.16 - 0.42)					
ED ₉₀ (range) 0.6(0.36 - 0.97)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 181

COMPOUND NAME

OR NUMBER ...PRIMAQUINE..... PARASITE (SUB)SPECIES ...*P. berghei*.....

FORMULATION ...Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >.5:0. MG/KG X .4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.3	5		-	87.5 ± 3.8
	1.0	5		-	83.6 ± 2.5
N	3.0	5	1	-	53.0 ± 11.2
	5.0	5		-	8.1 ± 4.2
	Ø	10		35.7	
ED ₅₀ (range) 1.6(0.8 - 4.3)					
ED ₉₀ (range) 6.0(3.0 - 16.0)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 185

COMPOUND NAME FLOXACRINE +

DR NUMBER PRIMAQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80./H₂O... ROUTE OF ADMINISTRATION : SC/HP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 0.3	5		-	86.2 ± 1.8
	0.3 + 0.3	5		-	74.9 ± 2.5
N	0.5 + 0.3	5	1	-	43.8 ± 6.0
	1.0 + 0.3	5		-	0.01 ± 0.01
	Ø	10		35.7	
ED ₅₀ (range) 0.25(0.14 - 0.5)					
ED ₉₀ (range) 0.4(0.22 - 0.8)					
Resistance factor I ₉₀					
	0.1 + 1.0	5		-	81.7 ± 4.7
	0.3 + 1.0	5		-	54.1 ± 5.4
N	0.5 + 1.0	5	1	-	20.6 ± 9.0
	1.0 + 1.0	5		-	0.3 ± 0.1
	Ø	10		35.7	
ED ₅₀ (range) 0.2(0.15 - 0.36)					
ED ₉₀ (range) 0.45(0.31 - 0.75)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 185

COMPOUND NAME FLOXACRINE +

OR NUMBER PRIMAQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION *Tween 80/H₂O*. ROUTE OF ADMINISTRATION : SC/~~IP~~/~~PO~~/~~IV~~

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 3.0	5		-	47.6 ± 10.1
	0.3 + 3.0	5		-	8.8 ± 8.2
N	0.5 + 3.0	5	1	-	0
	1.0 + 3.0	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) 0.13(0.08 - 0.21)					
ED ₉₀ (range) 0.2(0.13 - 0.33)					
Resistance factor I ₉₀					
	0.1 + 10.0	5		-	10.8 ± 7.2
	0.3 + 10.0	5		-	0.01 ± 0.01
N	0.5 + 10.0	5	1	-	0
	1.0 + 10.0	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) 0.06(0.04 - 0.07)					
ED ₉₀ (range) 0.1(0.07 - 0.12)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 187

COMPOUND NAME PRIMAQUINE +

OR NUMBER FLOXACRINE PARASITE (SUB)SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.3 + 0.1	5		-	86.2 ± 1.8
	1.0 + 0.1	5		-	81.7 ± 4.7
N	3.0 + 0.1	5	1	-	47.6 ± 10.1
	10.0 + 0.1	5		-	10.8 ± 7.2
	Ø	10		35.7	
ED ₅₀ (range) 1.6 (0.9 - 3.1)					
ED ₉₀ (range) 7.2 (4.2 - 14.0)					
Resistance factor I ₉₀					
	0.3 + 0.3	5		-	74.9 ± 2.5
	1.0 + 0.3	5		-	54.1 ± 5.4
N	3.0 + 0.3	5	1	-	8.8 ± 8.2
	10.0 + 0.3	5		-	0.01 ± 0.0
	Ø	10		35.7	
ED ₅₀ (range) 0.65 (0.44 - 1.2)					
ED ₉₀ (range) 1.3 (1.2 - 3.3)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 183

COMPOUND NAME PRIMAQUINE +

OR NUMBER FLOXACRINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.3 + 0.5	5		-	43.8 ± 6.0
	1.0 + 0.5	5		-	20.6 ± 9.0
N	3.0 + 0.5	5	1	-	0
	10.0 + 0.5	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) 0.4 (0.24 - 0.73)					
ED ₉₀ (range) 0.78 (0.47 - 1.4)					
Resistance factor I ₉₀					
	0.3 + 1.0	5		-	0.01 ± 0.01
	1.0 + 1.0	5		-	0.3 ± 0.1
N	3.0 + 1.0	5	1	-	0
	10.0 + 1.0	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) < 0.3					
ED ₉₀ (range) < 0.3					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 183

COMPOUND NAME

OR NUMBER ..FLOXACRINE..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/HP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >100... MG/KG X .4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.1	5		-	80.4 ± 2.3
	0.3	5		-	64.5 ± 5.1
N	0.5	5	1	-	28.3 ± 8.7
	1.0	5		-	1.0 ± 0.5
	∅	10		35.7	
ED ₅₀ (range) 0.25(0.16 - 0.42)					
ED ₉₀ (range) 0.6(0.36 - 0.97)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 190

COMPOUND NAME

OR NUMBER ... CHLOROQUINE ... PARASITE (SUB)SPECIES ... *P. berghei* ...

FORMULATION ... Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ... 10.0 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.3	5		-	68.7 ± 4.8
	1.0	5		-	66.6 ± 6.3
N	3.0	5	1	-	23.5 ± 2.7
	10.0	5		-	0.01 ± 0.01
	∅	10		35.7	
ED ₅₀ (range) 1.4 (1.1 - 2.2)					
ED ₉₀ (range) 2.7 (2.1 - 4.1)					
Resistance factor I ₉₀					
ED ₅₀ (range)					
ED ₉₀ (range)					
Resistance factor I ₉₀					

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

-TABLE 191

COMPOUND NAME FLOXACRINE +

OR NUMBER CHLOROQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80, H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 0.3	5		-	78.6 ± 8.3
	0.3 + 0.3	5		-	45.7 ± 4.2
N	0.5 + 0.3	5	1	-	20.6 ± 8.0
	1.0 + 0.3	5		-	4.3 ± 3.5
	Ø	10		35.7	
ED ₅₀ (range) 0.22 (0.12 - 0.3)					
ED ₉₀ (range) 0.7 (0.4 - 0.95)					
Resistance factor I ₉₀					
	0.1 + 1.0	5		-	75.5 ± 2.2
	0.3 + 1.0	5		-	50.9 ± 4.5
N	0.5 + 1.0	5	1	-	11.2 ± 4.3
	1.0 + 1.0	5		-	1.1 ± 0.9
	Ø	10		35.7	
ED ₅₀ (range) 0.22 (0.14 - 0.33)					
ED ₉₀ (range) 0.49 (0.31 - 0.74)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 192

COMPOUND NAME FLOXACRINE +

OR NUMBER .CHLOROQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION ..Tween 80./H₂O.. ROUTE OF ADMINISTRATION : SC/~~IP~~/~~PO~~/~~IV~~

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.1 + 3.0	5		-	35.7 ± 4.1
	0.3 + 3.0	5		-	26.0 ± 2.4
N	0.5 + 3.0	5	1	-	1.2 ± 0.6
	1.0 + 3.0	5		-	0.4 ± 0.2
	Ø	10		35.7	
ED ₅₀ (range) 0.08(0.04-0.17)					
ED ₉₀ (range) 0.26(0.15-0.56)					
Resistance factor I ₉₀					
	0.1 + 10.0	5		-	0.06 ± 0.05
	0.3 + 10.0	5		-	0
N	0.5 + 10.0	5	1	-	0
	1.0 + 10.0	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) < 0.1					
ED ₉₀ (range) < 0.1					
Resistance factor I ₉₀					

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 193

COMPOUND NAME CHLOROQUINE +

OR NUMBER .FLOXACRINE..... PARASITE (SUB)SPECIES ...P. berghei.....

FORMULATION ..Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/TP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.3 + 0.1	5		-	78.6 ± 8.3
	1.0 + 0.1	5		-	75.5 ± 2.2
N	3.0 + 0.1	5	1	-	35.7 ± 4.1
	10.0 + 0.1	5		-	0.06 ± 0.05
	Ø	10		35.7	
ED ₅₀ (range) 1.8 (1.2 - 2.6)					
ED ₉₀ (range) 3.6 (2.5 - 5.2)					
Resistance factor I ₉₀					
	0.3 + 0.3	5		-	45.7 ± 4.2
	1.0 + 0.3	5		-	50.9 ± 4.5
N	3.0 + 0.3	5	1	-	26.0 ± 2.4
	10.0 + 0.3	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) 1.3 (0.9 - 2.2)					
ED ₉₀ (range) 2.6 (1.8 - 4.3)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 191

COMPOUND NAME CHLOROQUINE +

OR NUMBER . FLOXARINE..... PARASITE (SUB)SPECIES . *P. berghei*.....

FORMULATION ... Tween 80 / H₂O .. ROUTE OF ADMINISTRATION : SC / IP / PO / IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% ^{x100}
	0.3 + 0.5	5		-	20.6 ± 8.0
	1.0 + 0.5	5		-	11.2 ± 4.3
N	3.0 + 0.5	5	1	-	1.2 ± 0.6
	10.0 + 0.5	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) 0.17 (0.03 - 0.33)					
ED ₉₀ (range) 0.7 (0.33 - 1.3)					
Resistance factor I ₉₀					
	0.3 + 1.0	5		-	43 ± 3.5
	1.0 + 1.0	5		-	1.1 ± 0.9
N	3.0 + 1.0	5	1	-	0.4 ± 0.2
	10.0 + 1.0	5		-	0
	Ø	10		35.7	
ED ₅₀ (range) 0.03 (0.01 - 0.06)					
ED ₉₀ (range) 0.2 (0.05 - 0.4)					
Resistance factor I ₉₀					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

5.6 DRUG INTERACTION ISOBOLOGRAMS

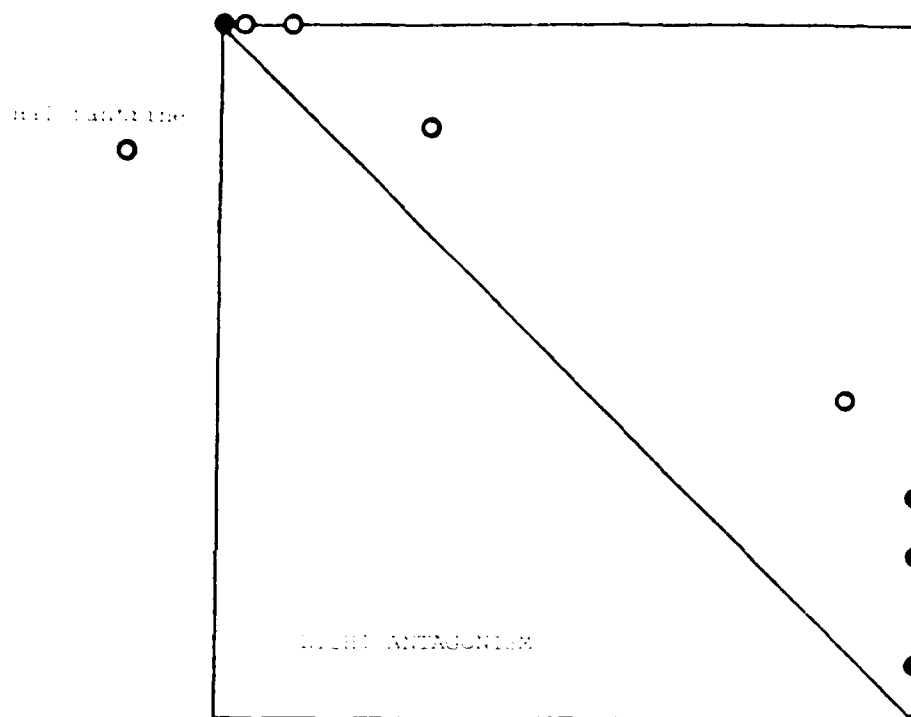


Figure 1

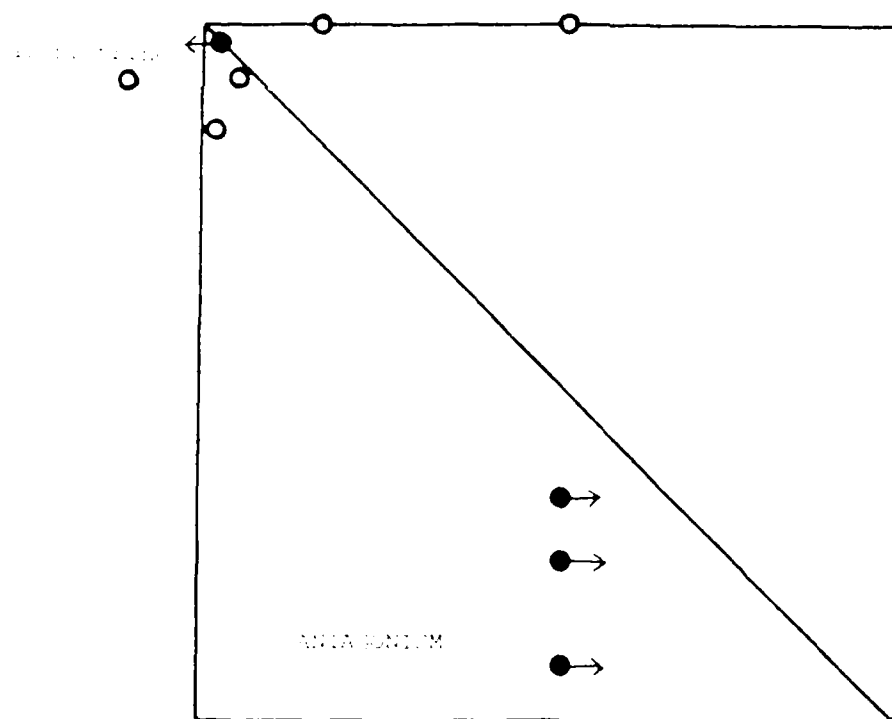


Figure 2

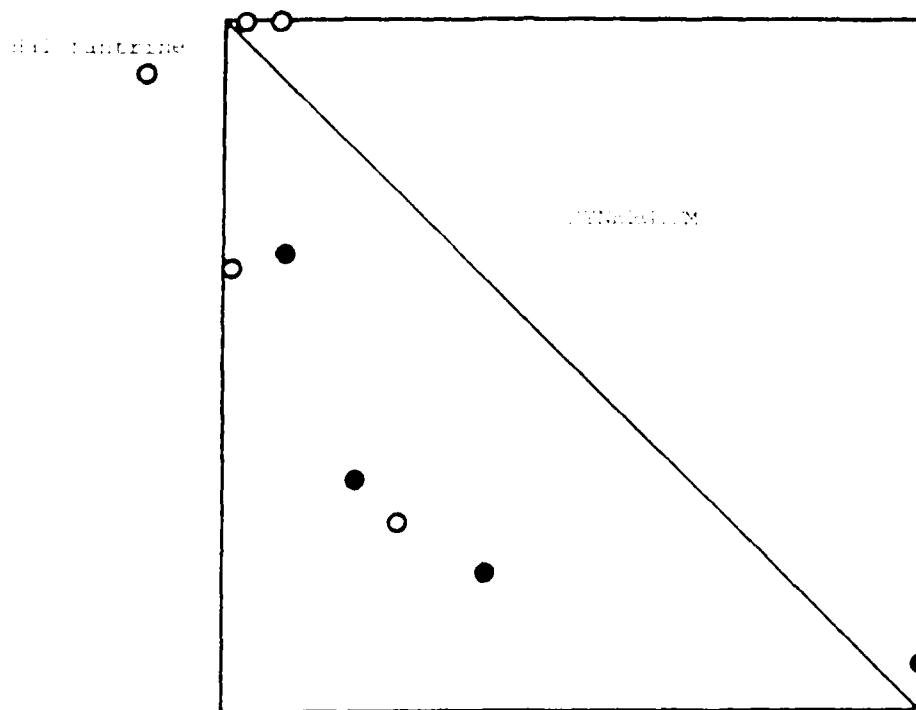


Figure 3

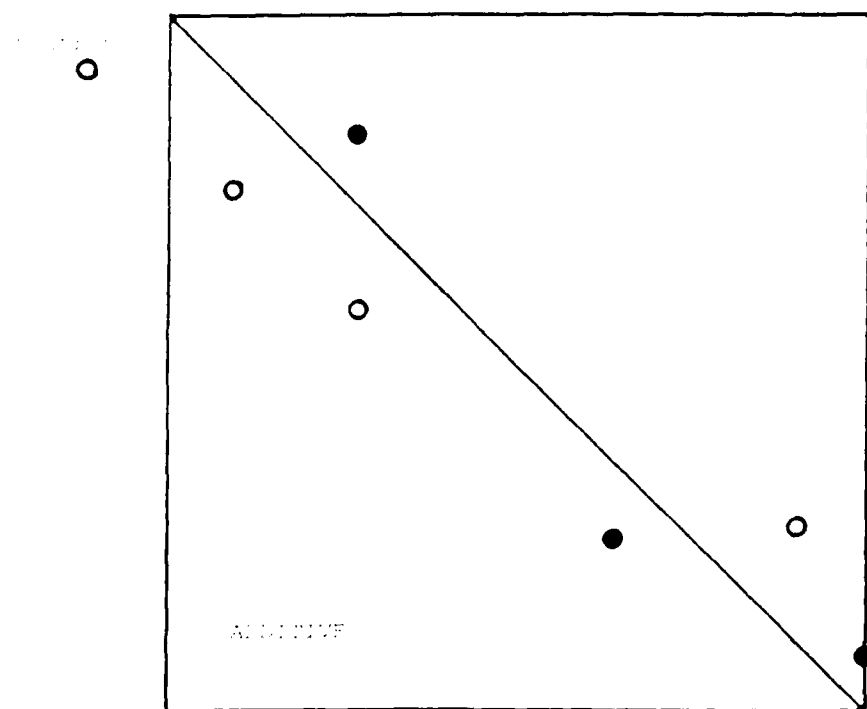


Figure 4

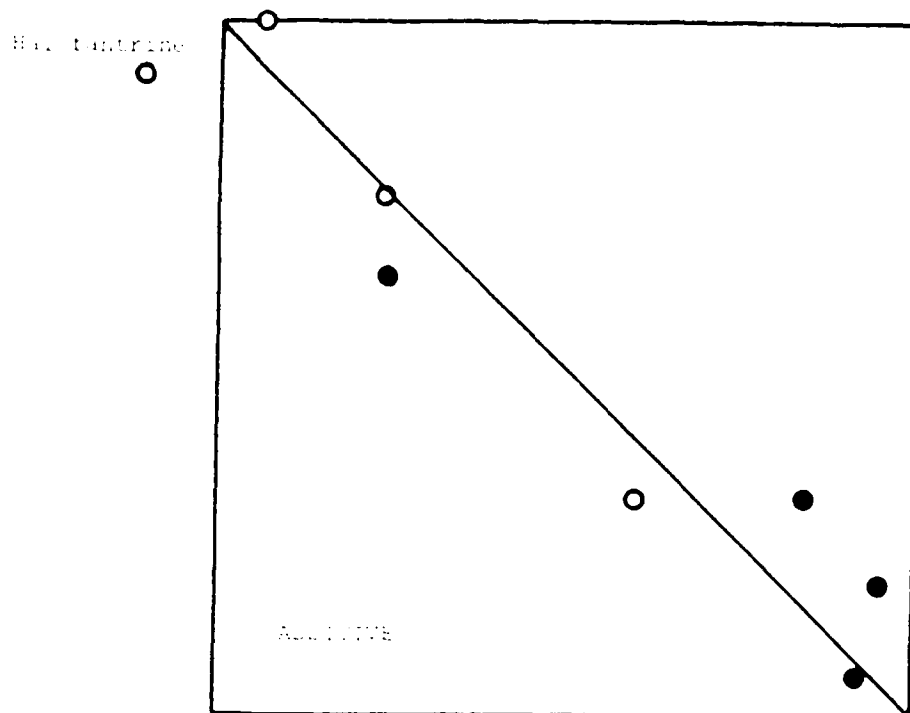


Figure 5

Stimulating

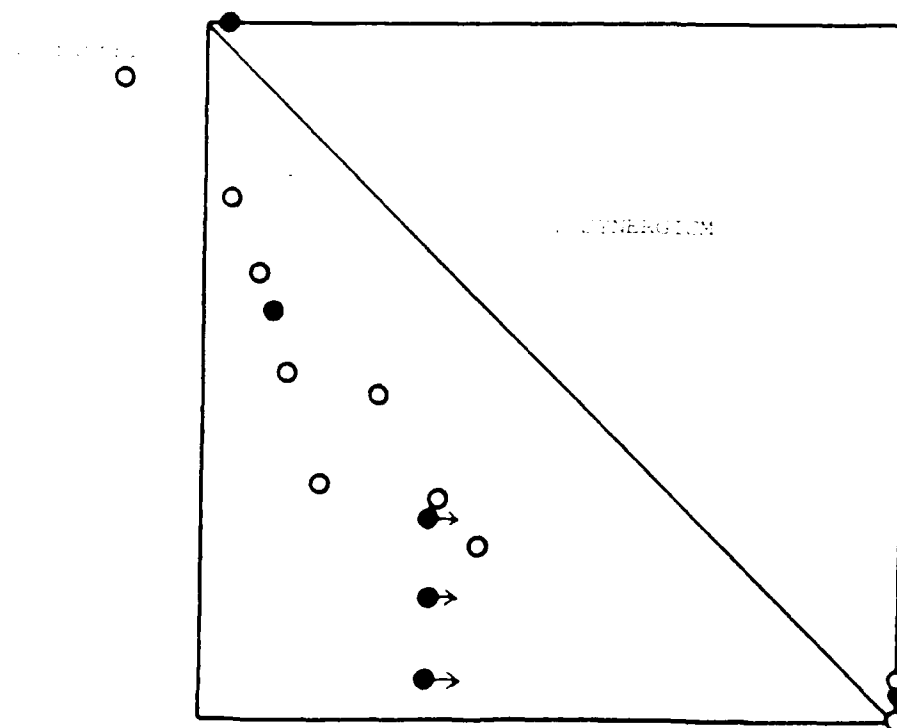


Figure 6

Stimulating

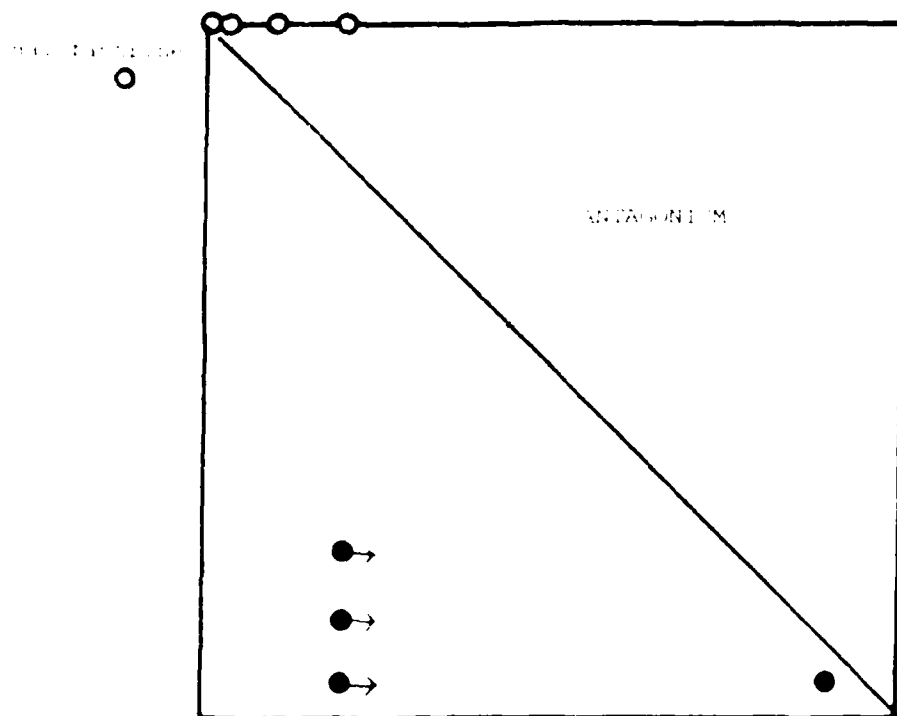


Figure 7

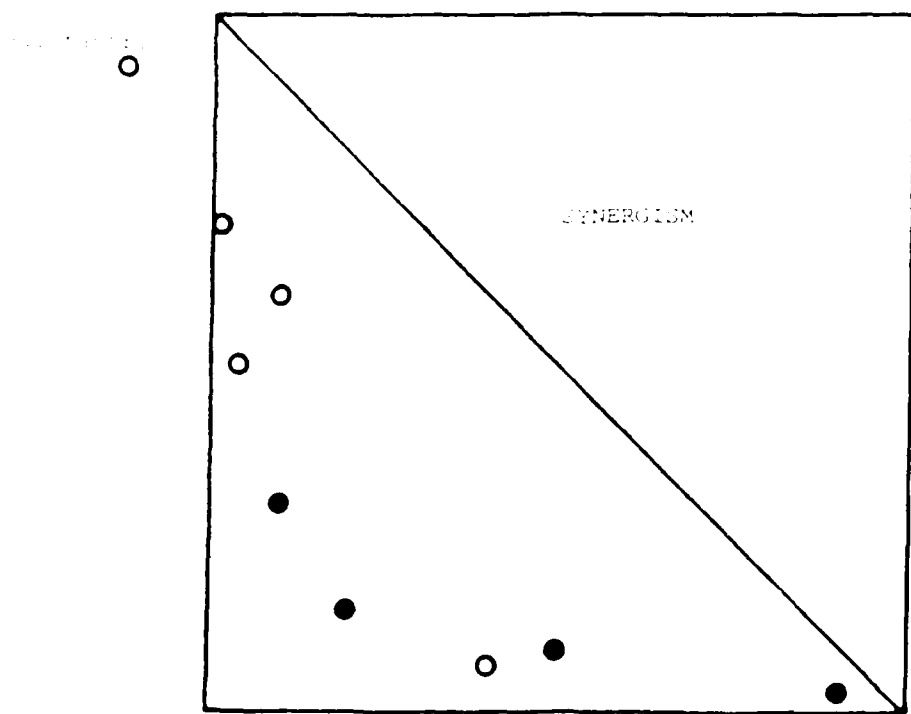


Figure 8

Figure 9

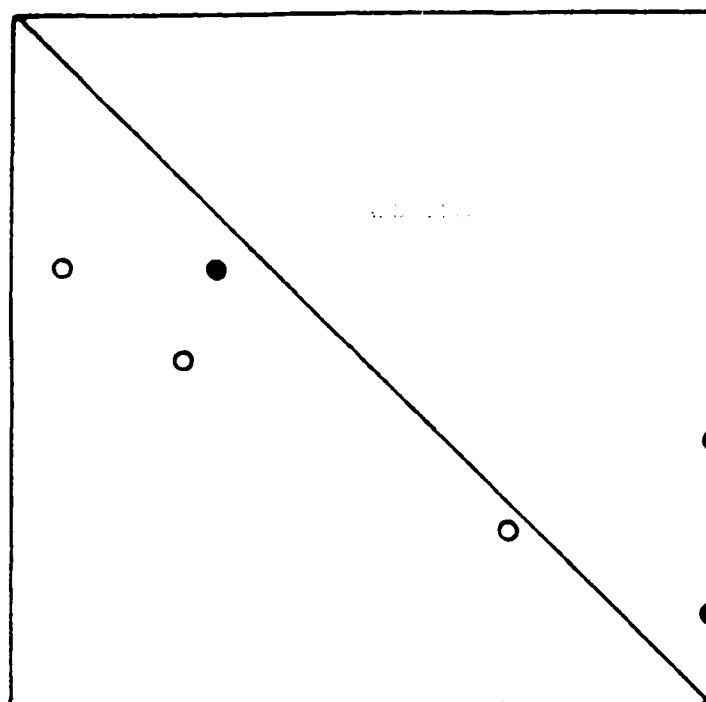


Figure 9

Figure 10

Figure 10

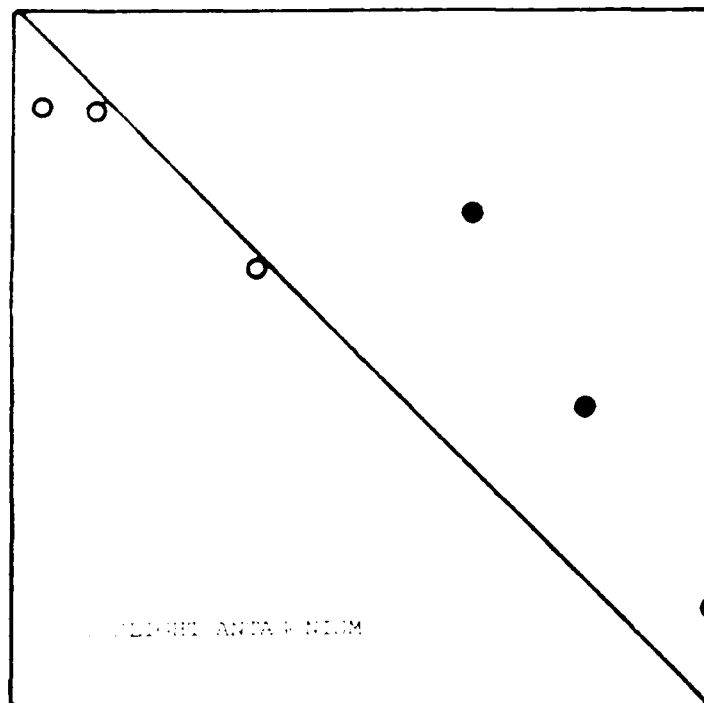


Figure 10

Figure 10

Figure 11

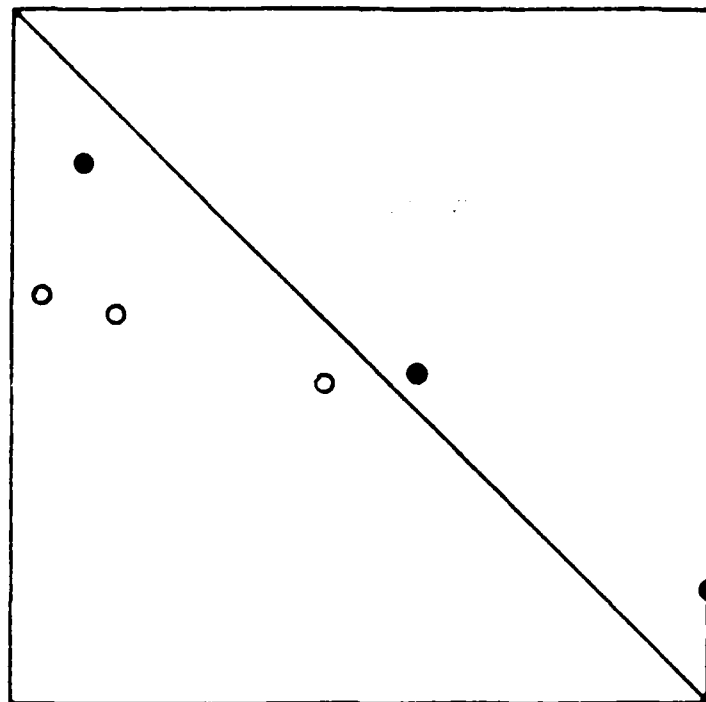


Figure 11

Figure 12

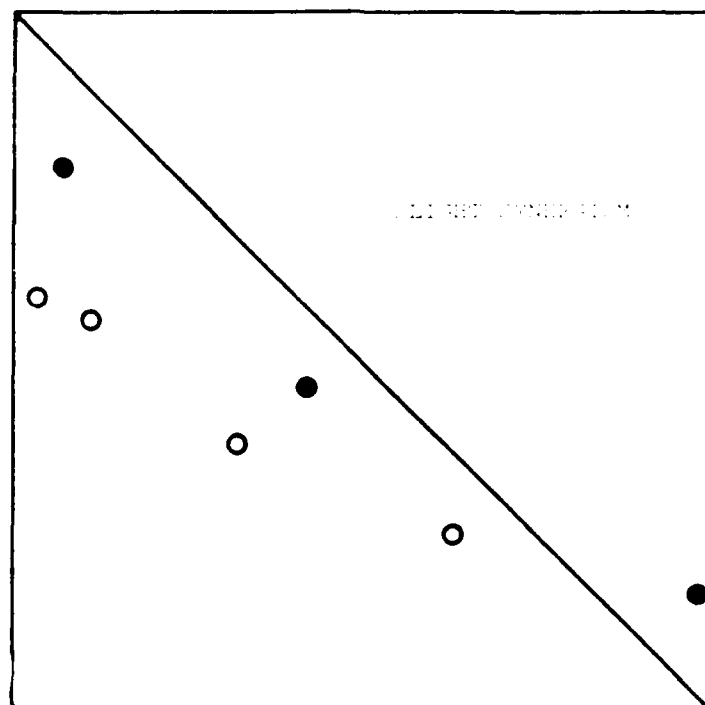


Figure 12

Figure 12

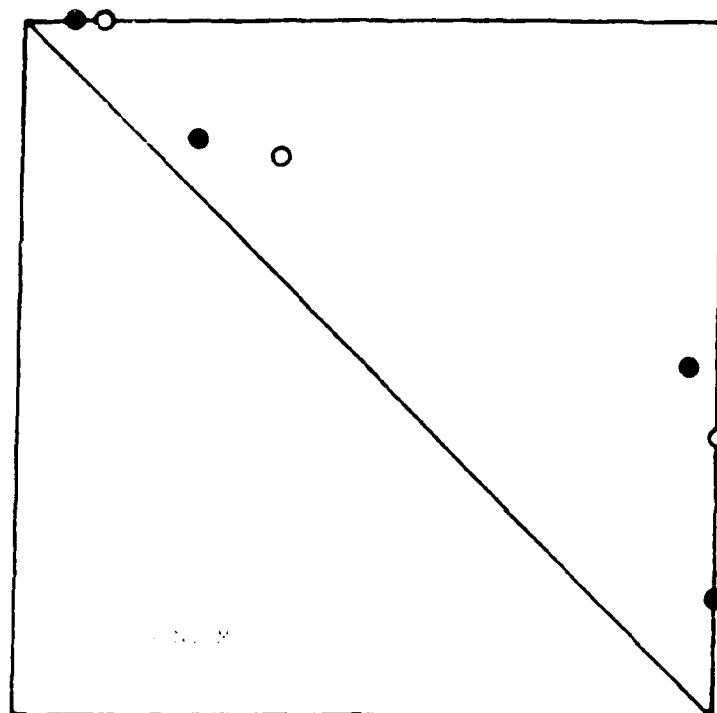


Figure 1b

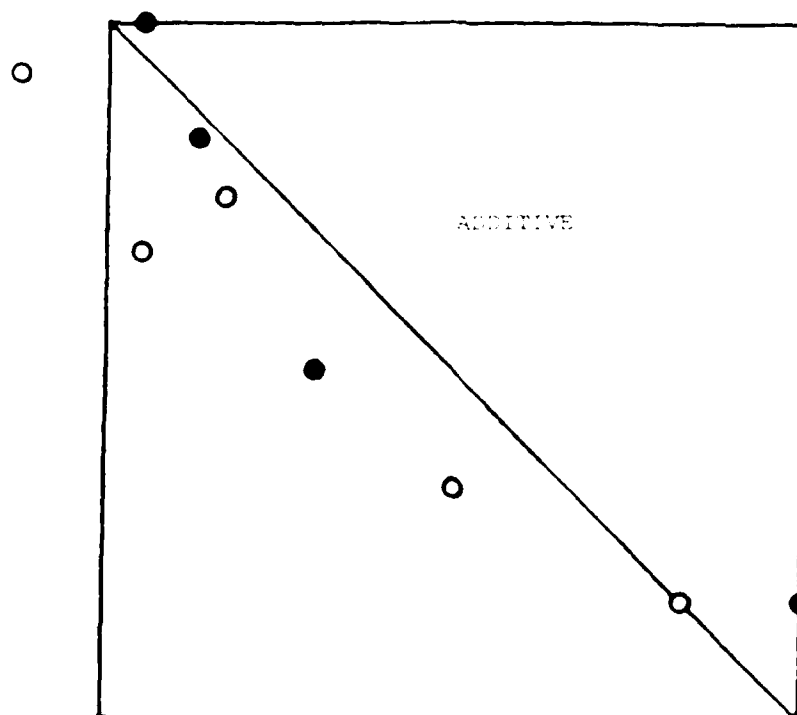
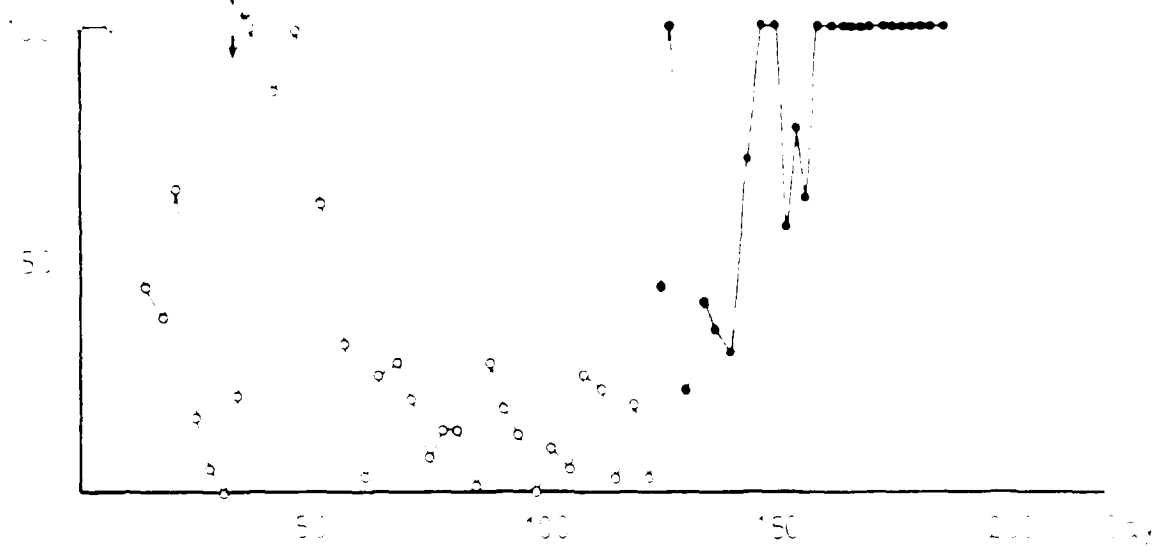


Figure 1c

5.7 ACQUISITION OF RESISTANCE GRAPHS

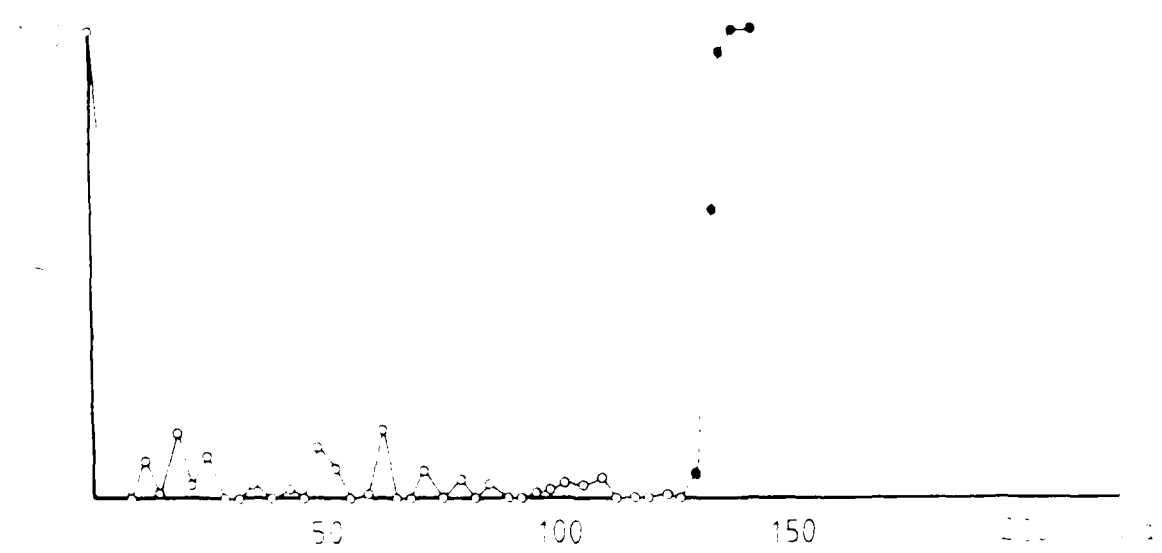
% Passage
Delay

NS-4₁
Halothane 8m₂ 100%



% Passage
Delay

NS-4₁
Halothane 30m₂ 100%

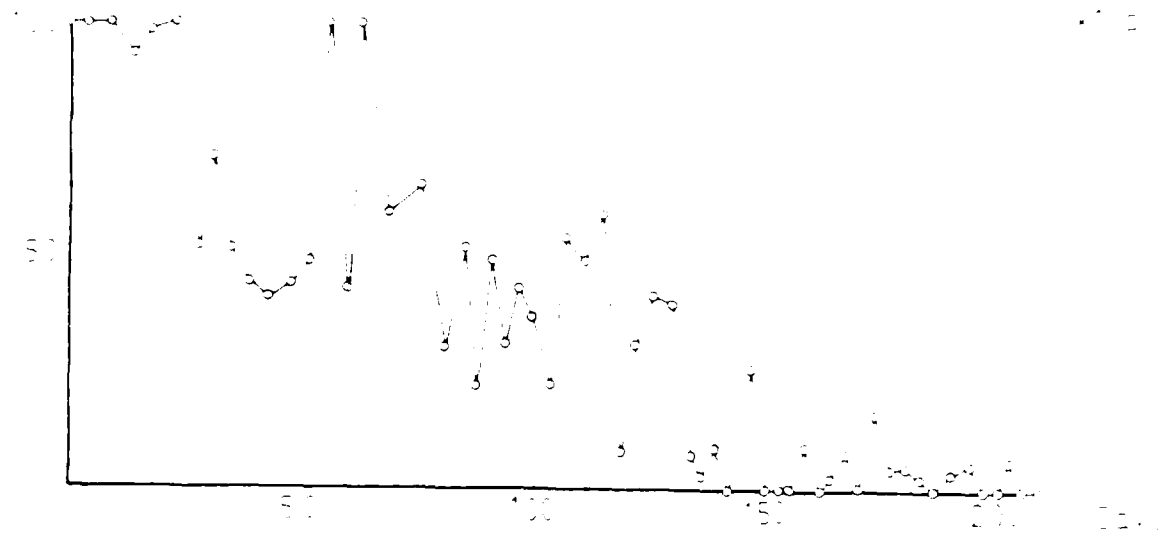


Passage 1

Dea.

1923

June 10, 1923



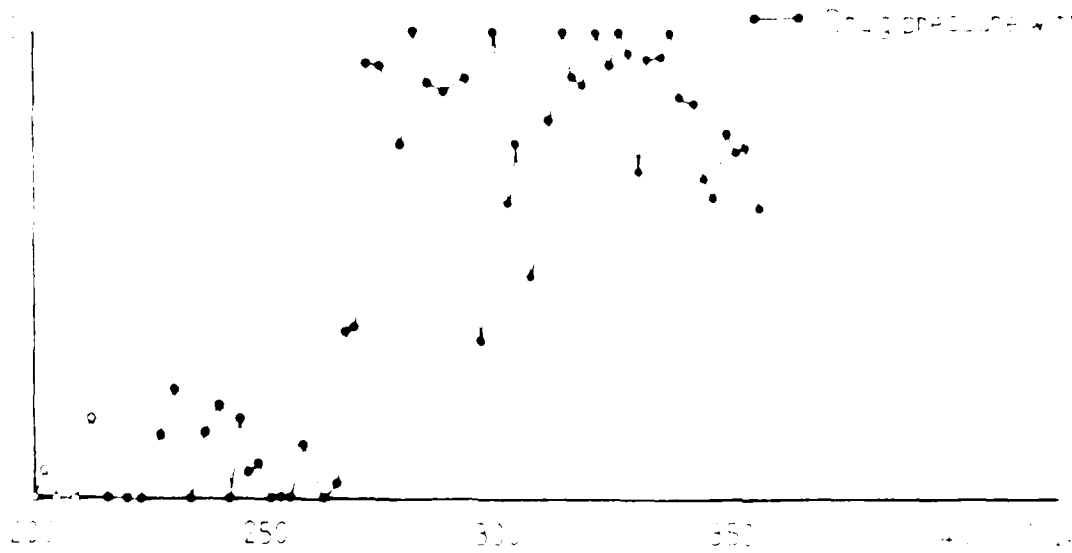
Passage 1

Dea.

1923

Under drug pressure

Drug pressure with work



5. - FIVE DAY TEST DATA NEW RESISTANT LINES

SUMMARY OF ANTIMALARIAL DRUG TESTS

Table 198

SINGLE THERAPEUTIC DOSE

COMPOUND NAME

DR NUMBER

HALOFANTRINE

PARASITE (SUB)SPECIES

P. berghei

FORMULATION

Tween 80 / H₂O

ROUTE OF ADMINISTRATION :

SC/IP/PQ/IV

MAXIMUM TOLERATED DOSE (MTD)

>30 MG/KG X 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR ₂₋₁₀ Control PR ₂₋₁₀
	0.1	5		-	94.8 ± 5.2
	0.3	5		-	91.4 ± 2.0
N	1.0	5	1	-	51.6 ± 14.1
	3.0	5		-	0.1 ± 0.1
	Ø	10		20.9	
ED ₅₀ (range) 0.5 (0.1 - 1.3)					
ED ₉₀ (range) 1.3 (0.4 - 3.5)					
Resistance factor I ₉₀ 1.0					
	0.3	5		-	84.3 ± 3.9
	1.0	5		-	74.2 ± 9.6
N/HAL	3.0	5	1	-	44.4 ± 13.1
Pass. 31	10.0	5		-	0.1 ± 0.1
	30.0	5		-	0.02 ± 0.01
	Ø	10		23.9	
ED ₅₀ (range) 1.1 (0.4 - 2.8)					
ED ₉₀ (range) 3.6 (1.1 - 9.0)					
Resistance factor I ₉₀ 2.8					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

-TABLE 197

BUTHE (CHIT) MEDICINE

COMPOUND NAME

DR NUMBER CHLOROQUINE PARASITE (SUB)SPECIES ... *P. berghei*FORMULATION ... Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC/1P/P0/17MAXIMUM TOLERATED DOSE (MTD) ≥ 100 .. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% $\times 100$
	0.1	5		-	82.8 \pm 4.1
	0.3	5		-	80.1 \pm 5.7
N	1.0	5	1	-	52.1 \pm 7.6
	3.0	5		-	24.3 \pm 8.5
	\emptyset	10		20.9	
ED ₅₀ (range) 0.8(0.2 - 2.1)					
ED ₉₀ (range) 3.1(0.9 - 8.5)					
Resistance factor I ₉₀ 1.0					
	1.0	5		-	91.4 \pm 3.9
	3.0	5		-	53.6 \pm 8.9
N/HAL	10.0	5	1	-	0.8 \pm 0.3
Pass. 31	30.0	5		-	0.08 \pm 0.08
	\emptyset	10		23.9	
ED ₅₀ (range) 2.7(1.4 - 3.9)					
ED ₉₀ (range) 7.0(3.6 - 10.3)					
Resistance factor I ₉₀ 2.3					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

- JAN - 1958

BLOOD FILM AT 72 H

COMPOUND NAME

DR NUMBER ... PRIMAQUINE ... PARASITE (SUB) SPECIES *P. berghei* ...FORMULATION Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC/1P-25-14MAXIMUM TOLERATED DOSE (MTD) ≥ 60.0 MG/KG X 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% (100)
	0.1	5		-	92.5 \pm 3.6
	0.3	5		-	93.1 \pm 2.4
N	1.0	5	1	-	63.0 \pm 5.1
	3.0	5		-	34.4 \pm 4.0
	10.0	5		-	0
	\emptyset	10		20.9	
ED ₅₀ (range) 1.5 (1.1 - 2.2)					
ED ₉₀ (range) 5.8 (4.1 - 8.4)					
Resistance factor I ₉₀ 1.0					
	1.0	5		-	77.6 \pm 4.8
	3.0	5		-	68.1 \pm 8.0
N/HAL	10.0	5	1	-	14.7 \pm 7.8
Pass 31	30.0	5		-	0.3 \pm 0.07
	60.0	5		-	0.03 \pm 0.01
	\emptyset	10		23.9	
ED ₅₀ (range) 2.9 (1.6 - 6.0)					
ED ₉₀ (range) 10.5 (5.6 - 23.0)					
Resistance factor I ₉₀ 1.8					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

IN VIVO SCHIZONTICIDES

COMPOUND NAME

DR NUMBER

MEFLOQUINE

PARASITE (SUB)SPECIES

*P. berghei*FORMULATION *Tween 80/H₂O* ROUTE OF ADMINISTRATION : SC ~~AD-PO, IV~~MAXIMUM TOLERATED DOSE (MTD) *>.60*... MG/KG X *4*.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR% x 100
	0.3	5		-	100 ± 7.1
	1.0	5		-	85.9 ± 2.3
N	3.0	5	1	-	17.4 ± 5.2
	10.0	5		-	0
	Ø	10		20.9	

ED₅₀(range) 1.6(0.5 - 2.2)ED₉₀(range) 2.8(0.9 - 3.7)Resistance factor I₉₀ 1.0

	1.0	5		-	87.5 ± 3.8
	3.0	5		-	73.8 ± 6.3
N/HAL	10.0	5	1	-	25.8 ± 4.8
Pass. 31	30.0	5		-	0.1 ± 0.08
	60.0	10		-	0
	Ø	10		23.9	

ED₅₀(range) 3.4(2.2 - 6.5)ED₉₀(range) 9.0(5.8 - 18.0)Resistance factor I₉₀ 3.2

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

TABLE 200

BLIND SCHISTOSOMIASIS

COMPOUND NAME

OR NUMBER ... QUININE ... PARASITE (SUB)SPECIES ... *P. berghei* ...FORMULATION ... Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC-IT-PO-IT

MAXIMUM TOLERATED DOSE (MTD) > 600.0 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated F ₁ % Control F ₁ %
	10.0	5		-	98.2 ± 2.7
	30.0	5		-	61.3 ± 7.3
N	100.0	5	1	-	36.1 ± 7.8
	300.0	5		-	0
	Ø	10		25.3	
ED ₅₀ (range) 45.0(23.0-90.0)					
ED ₉₀ (range) 85.0(43.0-175)					
Resistance factor I ₉₀ 1.0					
	30.0	5		-	86.1 ± 3.5
	100.0	5		-	48.9 ± 7.5
N/HAL	300.0	5	1	-	13.3 ± 9.3
Pass. 31	600.0	5		-	0.02 ± 0.01
	Ø	10		23.9	
ED ₅₀ (range) 90.0(55.0-180)					
ED ₉₀ (range) 210(125-420)					
Resistance factor I ₉₀ 2.5					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

- TAB. 201

B.L. 11. 1917. 11. 11. 11. 11. 11.

COMPOUND NAME

OR NUMBER ... HALOFANTRINE ... PARASITE (SUB)SPECIES *P. yoelii* ...FORMULATION *Tween 80 / H₂O* ROUTE OF ADMINISTRATION : SC/1P, 80, 11MAXIMUM TOLERATED DOSE (MTD) $2.100 \text{ MG/KG} \times .4$

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR%
	0.1	5		-	86.1 ± 2.6
	0.3	5		-	67.6 ± 6.1
NS	1.0	5	1	-	36.5 ± 10.5
	3.0	5		-	1.6 ± 0.6
	10.0	5		-	0.02 ± 0.01
	30.0	5		-	0
	\emptyset	10		24.4	
ED ₅₀ (range) 0.4 (0.3 - 1.0)					
ED ₉₀ (range) 1.6 (0.9 - 3.5)					
Resistance factor I ₉₀ 1.0					
	3.0	5		-	98.8 ± 3.0
	10.0	5		-	90.0 ± 4.1
NS/HAL	30.0	5	1	-	87.3 ± 2.4
Pass.35	100.0	5		-	46.4 ± 9.8
	\emptyset	10		10.2	
ED ₅₀ (range) 85.0 (48.0 - 118)					
ED ₉₀ (range) 560 (320 - 780)					
Resistance factor I ₉₀ 350					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

COMPOUND NAME

DR NUMBER ... CHLOROQUINE ... PARASITE (SUB)SPECIES ... *P. yoelii* ...FORMULATION ... Tween 80 / H₂O ... ROUTE OF ADMINISTRATION : SC ~~IP~~ IV

MAXIMUM TOLERATED DOSE (MTD) > 100. MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated MTD control rate
	1.0	5		-	81.1 ± 9.6
	3.0	5		-	54.9 ± 6.7
NS	10.0	5	1	-	24.9 ± 5.7
	30.0	5		-	18.0 ± 6.5
	60.0	5		-	9.4 ± 1.3
	Ø	10		24.4	
ED ₅₀ (range) 4.7(2.2-120)					
ED ₉₀ (range) 42.0(19.0-108)					
Resistance factor I ₉₀ 1.0					
	10.0	5		-	100
	30.0	5		-	100 ± 4.5
NS/HAL	60.0	5	1	-	86.1 ± 7.7
Pass 35	100.0	5		-	85.1 ± 2.4
	Ø	10		10.2	
ED ₅₀ (range) > 100					
ED ₉₀ (range) >> 100					
Resistance factor I ₉₀ >> 2.4					

Principal Investigator: Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

Date: 1961.11.10

MEDICAL NAME

DRUG NAME: PRIMAQUINE PARASITE (SUB SPECIES): *Pyopelli*FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: SC ~~1-15-17~~

MAXIMUM TOLERATED DOSE (MTD): >60.0 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PPR Control PPR
	1.0	5		-	91.0 ± 5.1
	3.0	5		-	78.0 ± 10.3
NS	10.0	5	1	-	7.0 ± 2.5
	30.0	5		-	0
	Ø	10		29.2	
ED ₅₀ (range) 3.4 (2.0-6.0)					
ED ₂₀ (range) 7.0 (4.1-12.6)					
Resistance factor I ₉₀ 1.0					
	3.0	5		-	92.2 ± 8.3
	10.0	5		-	79.3 ± 7.0
NS/HAL	30.0	5	1	-	0.2 ± 0.2
Pass 35	60.0	5		-	0.04 ± 0.02
	Ø	10		10.2	
ED ₅₀ (range) 7.0 (2.7-19.8)					
ED ₂₀ (range) 16.0 (6.0-44.0)					
Resistance factor I ₉₀ 2.3					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SAMPLE NAME

DRUG NAME: MEFLOQUINE

Pygoell

FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: ~~oral~~

MAXIMUM TOLERATED DOSE (MTD): >60.0 mg/kg x 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Control %
	3.0	5		-	70.8 ± 5.0
	10.0	5		-	14.1 ± 9.5
NS	30.0	5	1	-	0.07 ± 0.07
	100.0	5		-	0
	Ø	10		29.2	
ED ₅₀ (range) 4.4 (3.4-6.0)					
ED ₉₀ (range) 10.0 (7.8-14.0)					
Resistance factor I ₉₀ 1.0					
	3.0	5		-	92.8 ± 9.8
	10.0	5		-	100.0 ± 3.0
NS/HAL	30.0	5	1	-	100.0 ± 3.0
Pass 35	60.0	5		-	94.3 ± 3.2
	Ø	10		10.2	
ED ₅₀ (range) >> 60					
ED ₉₀ (range) >> 60					
Resistance factor I ₉₀ >> 10					

Principal Investigator: Professor W. Jeter

Department of Medical Protozoology

London School of Hygiene & Tropical Medicine

QUININE AND METIDOL

MEDICAL NAME

DRUG NAME: QUININE PARASITE (SUB)SPECIES: *P. berghei*FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: ~~SC~~ IP \pm

MAXIMUM TOLERATED DOSE (MTD) >600 MG/KG X 4.

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Mean % Control (SE)
	3.0	5		-	100 \pm 0.1
	10.0	5		-	77.8 \pm 11.9
NS	30.0	5	1	-	67.3 \pm 13.0
	100.0	5		-	52.6 \pm 3.8
	300.0	5		-	9.1 \pm 4.6
	600.0	5		-	0.2 \pm 0.2
	\emptyset	10		19.6	

ED₅₀ (range) 46.0 (11.0-95.0)ED₃₀ (range) 190.0 (45.0-390.0)Resistance factor I₉₀ 1.0

	100.0	5		-	100 \pm 2.3
	300.0	5		-	98.8 \pm 1.3
NS/HAL	600.0	5		-	91.7 \pm 5.5
Pass. 35	\emptyset	10		10.2	

ED₅₀ (range) >600ED₃₀ (range) >>600Resistance factor I₃₀ >>3.2

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SUMMARY OF ANTIMALARIAL DRUG TESTS

-1961-208

BLOOD-LEVEL ANTICLONAL

COMPOUND NAME

DR NUMBER

HALOFANTRINE.....

PARASITE (SUB)SPECIES

P. berghei.....

FORMULATION

Tween 80/H₂O

ROUTE OF ADMINISTRATION : SC/IP/PQ/IT

MAXIMUM TOLERATED DOSE (MTD)

>30... MG/KG X .4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PPE Control PPE
	0.1	5		-	94.8 ± 5.2
	0.3	5		-	91.4 ± 2.0
N	1.0	5	1	-	51.6 ± 14.1
	3.0	5		-	0.1 ± 0.1
	Ø	10		20.9	
ED ₅₀ (range) 0.5 (0.1 - 1.3)					
ED ₉₀ (range) 1.3 (0.4 - 3.5)					
Resistance factor I ₉₀ 1.0					
	1.0	5		-	87.5 ± 6.2
	3.0	5		-	86.5 ± 16.3
N/1923	10.0	5	1	-	91.5 ± 3.1
(R ₁₅ , 56)	30.0	5		-	100 ± 2.2
	100.0	5		-	80.3 ± 11.8
	Ø	10		S.C	
ED ₅₀ (range) > 100					
ED ₉₀ (range) > 100					
Resistance factor I ₉₀ > 77					

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COMPOUND NAME

CP NUMBER CHLOROQUINE

FORMULATION Triclin. SC/H₂O ROUTE OF ADMINISTRATION

MAXIMUM TOLERATED DOSE MTD >1000 mg/kg (9)

Strain	Daily dose mg/kg DO-0+3	No. of mice	No. of experiments	Mean (range) parasite rate %	Standard error
	0.1	5		-	8.5 ± 4.1
	0.3	5		-	80.1 ± 5.9
N	1.0	5	1	-	52.1 ± 7.6
	3.0	5		-	24.3 ± 8.5
	∅	10		20.0	

ED₅₀(range) 0.8 (0.2-2.1)

ED₉₀(range) 3.1 (0.9-8.5)

Resistance factor I₉₀

	3.0	5		-	94.5 ± 4.0
	10.0	5		-	91.8 ± 4.1
N/1923	30.0	5	1	-	91.8 ± 7.4
(Pass 56)	60.0	5		-	100 ± 5.5
	∅	10		S.C.	

ED₅₀(range) > 60

ED₉₀(range) > 60

Resistance factor I₉₀ > 19

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PRIMAQUINE 100 mg tablets Plavix.

MAXIMUM TOLERATED DOSE (MTD) = 600 MG/KG X 4

EC ₅₀ (range): 1.5 (1.1 - 2.2)					
EC ₃₀ (range): 5.8 (4.1 - 8.4)					
Resistance factor I ₉₀ 1.0					
	30 °C	5		-	55.0 ± 4.7
	10 °C	5		-	34.0 ± 13.1
N ₁ 1923	30 °C	5	1	-	9.5 ± 4.3
(Pass 56)	10 °C	5		-	0.3 ± 0.1
	Ø	10		5.0	

Resistance factor γ_{Rd} 3.2

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MEFLORINE

MEFLORINE PARASITE: *P. berghei*

Formulation: Tween 80/H₂O. ROUTE OF ADMINISTRATION: SC + IV

MAXIMUM TOLERATED DOSE (MTD): > 600 MG/KG X 5d

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Resistance factor Control = 100
	0.3	5		-	100 ± 7.1
	1.0	5		-	83.9 ± 1.5
N	3.0	5	1	-	174 ± 3.2
	10.0	5		-	C
	Ø	10		20.9	

ED ₅₀ range: 1.6 (0.5-2.2)
ED ₉₀ range: 2.8 (0.3-3.7)
Resistance factor I ₉₀ 1 C

	3.0	5		-	83.9 ± 7.4
	10.0	5		-	73.5 ± 13.0
N1923	30.0	5	1	-	97.5 ± 4.6
(Pass 56)	60.0	5		-	100
	Ø	10		8.0	

ED ₅₀ range: > 60
ED ₉₀ range: > 60
Resistance factor I ₉₀ > 21

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

MOUSE NAME

QUININE PARASITE SUBSPECIES *P. berghei*

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION ~~SC~~ IP

MAXIMUM TOLERATED DOSE (MTD) > 6000 MG/KG (ST)

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated parasite rate %
	1000	5		-	98.2 ± 2.7
	3000	5		-	61.3 ± 7.3
N	1000	5	1	-	36.1 ± 7.5
	3000	5		-	C
	0	10		25.3	

ED₅₀ (range) 45.0 (23.0-90.0)

ED₉₀ (range) 85.0 (43.0-175)

Resistance factor I₉₀ 1.0

	1000	5		-	55.0 ± 8.2
	3000	5		-	70.5 ± 8.4
N10023	6000	5	1	-	75.4 ± 23.1
(R ₅₀ 56)	0	10		8.0	

ED₅₀ (range) > 600

ED₉₀ (range) > 600

Resistance factor I₉₀ > 7.1

Principal Investigator: Professor W. Petri
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LIMED
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